



Edinburgh Research Explorer

Genetic correlation between amyotrophic lateral sclerosis and schizophrenia

Citation for published version:

McLaughlin, RL, Schijven, D, Van Rheenen, W, Van Eijk, KR, O'Brien, M, Kahn, RS, Ophoff, RA, Goris, A, Bradley, DG, Al-Chalabi, A, Van Den Berg, LH, Luykx, JJ, Hardiman, O, Veldink, JH, Shatunov, A, Dekker, AM, Diekstra, FP, Pulit, SL, Van Der Spek, RAA, Van Doormaal, PTC, Sproviero, W, Jones, AR, Nicholson, GA, Rowe, DB, Pamphlett, R, Kiernan, MC, Bauer, D, Kahlke, T, Williams, K, Eftimov, F, Fogh, I, Ticozzi, N, Lin, K, Millicamps, S, Salachas, F, Meininger, V, Carvalho, MD, Pinto, S, Mora, JS, Rojas-García, R, Polak, M, Chandran, S, Colville, S, Swingler, R, Morrison, KE, Shaw, PJ, Hardy, J, Orrell, RW, Pittman, A, Sidle, K, Fratta, P, Malaspina, A, Petri, S, Abdulla, S, Drepper, C, Sendtner, M, Meyer, T, Wiedau-Pazos, M, Lomen-Hoerth, C, Deerlin, VMV, Trojanowski, JQ, Elman, L, McCluskey, L, Basak, N, Meitinger, T, Lichtner, P, Blagojevic-Radivojkov, M, Andres, CR, Maurel, C, Bensimon, G, Landwehrmeyer, B, Brice, A, Payan, CAM, Saker-Delye, S, Durr, A, Wood, N, Tittmann, L, Lieb, W, Franke, A, Rietschel, M, Cichon, S, Nothen, MM, Amouyel, P, Tzourio, C, Dartigues, JF, Uitterlinden, AG, Rivadeneira, F, Estrada, K, Hofman, A, Curtis, C, Derkooi, AJV, De Visser, M, Weber, M, Shaw, CE, Smith, BN, Pansarasa, O, Cereda, C, Bo, RD, Comi, GP, D'Alfonso, S, Bertolin, C, Soraru, G, Mazzini, L, Pensato, V, Gellera, C, Tiloca, C, Ratti, A, Calvo, A, Moglia, C, Brunetti, M, Arcuti, S, Capozzo, R, Zecca, C, Lunetta, C, Penco, S, Riva, N, Padovani, A, Filosto, M, Blair, I, Nigel Leigh, P, Casale, F, Chio, A, Beghi, E, Pupillo, E, Tortelli, R, Logroscino, G, Powell, J, Ludolph, AC, Weishaupt, JH, Robberecht, W, Damme, PV, Brown, RH, Glass, J, Landers, JE, Andersen, PM, Corcia, P, Vourc'h, P, Silani, V, Es, MAV, Pasterkamp, RJ, Lewis, CM, Breen, G, Ripke, S, Neale, BM, Corvin, A, Walters, JTR, Farh, KH, Holmans, PA, Lee, P, Bulik-Sullivan, B, Collier, DA, Huang, H, Pers, TH, Agartz, I, Agerbo, E, Albus, M, Alexander, M, Amin, F, Bacanu, SA, Begemann, M, Belliveau, RA, Bene, J, Bergen, SE, Bevilacqua, E, Bigdeli, TB, Black, DW, Bruggeman, R, Buccola, NG, Buckner, RL, Byerley, W, Cahn, W, Cai, G, Campion, D, Cantor, RM, Carr, VJ, Carrera, N, Catts, SV, Chambert, KD, Chan, RCK, Chan, RYL, Chen, EYH, Cheng, W, Cheung, EFC, Chong, SA, Cloninger, CR, Cohen, D, Cohen, N, Cormican, P, Craddock, N, Crowley, JJ, Curtis, D, Davidson, M, Davis, KL, Degenhardt, F, Favero, JD, Demontis, D, Dikeos, D, Dinan, T, Djurovic, S, Donohoe, G, Drapeau, E, Duan, J, Dudbridge, F, Durmishi, N, Eichhammer, P, Eriksson, J, Escott-Price, V, Essioux, L, Fanous, AH, Farrell, MS, Frank, J, Franke, L, Freedman, R, Freimer, NB, Friedl, M, Friedman, JI, Fromer, M, Genovese, G, Georgieva, L, Giegling, I, Giusti-Rodríguez, P, Godard, S, Goldstein, JI, Golimbet, V, Gopal, S, Gratten, J, De Haan, L, Hammer, C, Hamshere, ML, Hansen, M, Hansen, T, Haroutunian, V, Hartmann, AM, Henskens, FA, Herms, S, Hirschhorn, JN, Hoffmann, P, Hofman, A, Hollegaard, MV, Hougaard, DM, Ikeda, M, Joa, I, Julia, A, Kalaydjieva, L, Karachanak-Yankova, S, Karjalainen, J, Kavanagh, D, Keller, MC, Kennedy, JL, Khrunin, A, Kim, Y, Klovins, J, Knowles, JA, Konte, B, Kucinskas, V, Kucinskiene, ZA, Kuzelova-Ptackova, H, Kahler, AK, Laurent, C, Lee, J, Hong Lee, S, Legge, SE, Lerer, B, Li, M, Li, T, Liang, KY, Lieberman, J, Limborska, S, Loughland, CM, Lubinski, J, Lonnqvist, J, MacEk, M, Magnusson, PKE, Maher, BS, Maier, W, Mallet, J, Marsal, S, Mattheisen, M, Mattingsdal, M, McCarley, RW, McDonald, C, McIntosh, AM, Meier, S, Meijer, CJ, Melegh, B, Melle, I, Meshulam-Gately, RI, Metspalu, A, Michie, PT, Milani, L, Milanova, V, Mokrab, Y, Morris, DW, Mors, O, Murphay, KC, Murray, RM, Myin-Germeys, I, Muller-Myhsok, B, Nelis, M, Nenadic, I, Nertney, DA, Nestadt, G, Nicodemus, KK, Nikitina-Zake, L, Nisenbaum, L, Nordin, A, O'Callaghan, E, O'Dushlaine, C, Anthony O'Neill, F, Oh, SY, Olincy, A, Olsen, L, Vanos, J, Pantelis, C, Papadimitriou, GN, Papiol, S, Parkhomenko, E, Pato, MT, Paunio, T, Pejovic-Milovancevic, M, Perkins, DO, Pietilainen, O, Pimm, J, Pocklington, AJ, Price, A, Pulver, AE, Purcell, SM, Quedsted, D, Rasmussen, HB, Reichenberg, A, Reimers, MA, Richards, AL, Roffman, JL, Roussos, P, Ruderfer, DM, Salomaa, V, Sanders, AR, Schall, U, Schubert, CR, Schulze, TG, Schwab, SG, Scolnick, EM, Scott, RJ, Seidman, LJ, Shi, J, Sigurdsson, E, Silagadze, T, Silverman, JM, Sim, K, Slominsky, P, Smoller, JW, So, HC, Spencer, CCA, Stah, EA, Stefansson, H, Steinberg, S, Stogmann, E, Straub, RE, Strengman, E, Strohmaier, J, Scott Stroup, T, Subramaniam, M, Suvisaari, J, Svrakic, DM, Szatkiewicz, JP, Söderman, E, Thirumalai, S, Toncheva, D, Tosato, S, Veijola, J, Waddington, J, Walsh, D, Wang, D, Wang, Q, Webb, BT, Weiser, M, Wildenauer, DB, Williams, NM, Williams, S, Witt, SH, Wolen, AR, Wong, EHM, Wormley, BK, Xi, HS, Zai, CC, Zheng, X, Zimprich, F, Wray, NR, Stefansson, K, Visscher, PM, Adolfsson, R, Andreassen, OA, Blackwood, DHR, Bramon, E, Buxbaum, JD, Børglum, AD, Darvasi, A, Domenici, E, Ehrenreich, H, Esko, T, Gejman, PV, Gil, M, Gurling, H, Hultman, CM, Iwata, N, Jablensky, AV, Jonsson, EG, Kendler, KS, Kirov, G, Knight, J, Lencz, T, Levinson, DF, Li, QS, Liu, J, Malhotra, AK, McCarroll, SA, McQuillin, A, Moran, JL, Mortensen, PB, Mowry, BJ, Owen, MJ, Palotie, A, Pato, CN, Petryshen, TL, Posthuma, D, Riley, BP, Rujescu, D, Sham, PC, Sklar, P, Clair, DS, Weinberger, DR, Wendland, JR, Werge, T, Daly, MJ, Sullivan, PF & O'Donovan, MC 2017, 'Genetic correlation between amyotrophic lateral sclerosis and schizophrenia', *Nature Communications*, vol. 8, 14774. <https://doi.org/10.1038/ncomms14774>



ARTICLE

Received 6 Jul 2016 | Accepted 3 Feb 2017 | Published 21 Mar 2017

DOI: 10.1038/ncomms14774

OPEN

Genetic correlation between amyotrophic lateral sclerosis and schizophrenia

Russell L. McLaughlin^{1,2,*}, Dick Schijven^{3,4,*}, Wouter van Rheenen³, Kristel R. van Eijk³, Margaret O'Brien¹, Project MinE GWAS Consortium[†], Schizophrenia Working Group of the Psychiatric Genomics Consortium[‡], René S. Kahn⁴, Roel A. Ophoff^{4,5,6}, An Goris⁷, Daniel G. Bradley², Ammar Al-Chalabi⁸, Leonard H. van den Berg³, Jurjen J. Luykx^{3,4,9,**}, Orla Hardiman^{2,**} & Jan H. Veldink^{3,**}

We have previously shown higher-than-expected rates of schizophrenia in relatives of patients with amyotrophic lateral sclerosis (ALS), suggesting an aetiological relationship between the diseases. Here, we investigate the genetic relationship between ALS and schizophrenia using genome-wide association study data from over 100,000 unique individuals. Using linkage disequilibrium score regression, we estimate the genetic correlation between ALS and schizophrenia to be 14.3% (7.05–21.6; $P = 1 \times 10^{-4}$) with schizophrenia polygenic risk scores explaining up to 0.12% of the variance in ALS ($P = 8.4 \times 10^{-7}$). A modest increase in comorbidity of ALS and schizophrenia is expected given these findings (odds ratio 1.08–1.26) but this would require very large studies to observe epidemiologically. We identify five potential novel ALS-associated loci using conditional false discovery rate analysis. It is likely that shared neurobiological mechanisms between these two disorders will engender novel hypotheses in future preclinical and clinical studies.

¹Academic Unit of Neurology, Trinity Biomedical Sciences Institute, Trinity College Dublin, Dublin D02 DK07, Republic of Ireland. ²Smurfit Institute of Genetics, Trinity College Dublin, Dublin D02 DK07, Republic of Ireland. ³Department of Neurology and Neurosurgery, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht 3584 CX, The Netherlands. ⁴Department of Psychiatry, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht 3584 CX, The Netherlands. ⁵Department of Human Genetics, David Geffen School of Medicine, University of California, Los Angeles, California 90095, USA. ⁶Center for Neurobehavioral Genetics, Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, California 90095, USA. ⁷Department of Neurosciences, Experimental Neurology and Leuven Research Institute for Neuroscience and Disease (LIND), KU Leuven—University of Leuven, Leuven B-3000, Belgium. ⁸Department of Basic and Clinical Neuroscience, Maurice Wohl Clinical Neuroscience Institute, King's College London, London WC2R 2LS, UK. ⁹Department of Psychiatry, Hospital Network Antwerp (ZNA) Stuivenberg and Sint Erasmus, Antwerp 2020, Belgium. * These authors contributed equally to this work. ** These authors jointly supervised this work. Correspondence and requests for materials should be addressed to R.L.M. (email: mclaughr@tcd.ie).

†A full list of Project MinE GWAS Consortium members appears at the end of the paper. ‡A full list of Schizophrenia Working Group of the Psychiatric Genomics Consortium members appears at the end of the paper.

Amyotrophic lateral sclerosis (ALS) is a late-onset neurodegenerative condition characterized by progressive loss of upper and lower motor neurons, leading to death from respiratory failure in 70% of patients within 3 years of symptom onset. Although ALS is often described as a primarily motor-system disease, extramotor involvement occurs in up to 50% of cases, with prominent executive and behavioural impairment, and behavioural variant frontotemporal dementia (FTD) in up to 14% of cases¹. A neuropsychiatric prodrome has been described in some people with ALS–FTD, and higher rates of schizophrenia and suicide have been reported in first and second degree relatives of those with ALS, particularly in kindreds associated with the *C9orf72* hexanucleotide repeat expansion². These clinical and epidemiological observations suggest that ALS and schizophrenia may share heritability.

ALS and schizophrenia both have high heritability estimates (0.65 and 0.64, respectively)^{3,4}; however the underlying genetic architectures of these heritable components appear to differ. Analysis of large genome-wide association study (GWAS) datasets has implicated over 100 independent risk loci for schizophrenia⁵ and estimated that a substantial proportion (23%) of the variance in underlying liability for schizophrenia is due to additive polygenic risk (many risk-increasing alleles of low individual effect combining to cause disease) conferred by common genetic variants⁶. This proportion, the single nucleotide polymorphism (SNP)-based heritability, is lower in ALS (8.2%), in which fewer than ten risk loci have been identified by GWAS⁷. Nevertheless, both diseases have polygenic components, but the extent to which they overlap has not been investigated.

Recently, methods to investigate overlap between polygenic traits using GWAS data have been developed^{8–10}. These methods assess either pleiotropy (identical genetic variants influencing both traits) or genetic correlation (identical alleles influencing both traits). Genetic correlation is related to heritability; for both measures, binary traits such as ALS and schizophrenia are typically modelled as extremes of an underlying continuous scale of liability to develop the trait. If two binary traits are genetically correlated, their liabilities covary, and this covariance is determined by both traits having identical risk alleles at overlapping risk loci. Studies of pleiotropy and genetic correlation have provided insights into the overlapping genetics of numerous traits and disorders, although none to date has implicated shared polygenic risk between neurodegenerative and neuropsychiatric disease. Here, we apply several techniques to identify and dissect the polygenic overlap between ALS and schizophrenia. We provide evidence for genetic correlation between the two disorders which is unlikely to be driven by diagnostic misclassification and we demonstrate a lack of polygenic overlap between ALS and other neuropsychiatric and neurological conditions, which could be due to limited power given the smaller cohort sizes for these studies.

Results

Genetic correlation between ALS and schizophrenia. To investigate the polygenic overlap between ALS and schizophrenia, we used individual-level and summary data from GWAS for ALS⁷ (36,052 individuals) and schizophrenia⁵ (79,845 individuals). At least 5,582 control individuals were common to both datasets, but for some cohorts included in the schizophrenia dataset this could not be ascertained so this number is likely to be higher. For ALS, we used summary data from both mixed linear model association testing¹¹ and meta-analysis of cohort-level logistic regression¹². We first used linkage disequilibrium (LD) score regression with ALS and schizophrenia summary statistics; this technique models, for polygenic traits, a linear relationship between a SNP's LD score (the amount of genetic variation that it captures) and its

GWAS test statistic¹³. This distinguishes confounding from polygenicity in GWAS inflation and the regression coefficient can be used to estimate the SNP-based heritability (h^2_g) for single traits¹³. In the bivariate case, the regression coefficient estimates genetic covariance (ρ_g) for pairs of traits, from which genetic correlation (r_g) is estimated⁸; these estimates are unaffected by sample overlap between traits. Using constrained intercept LD score regression with mixed linear model ALS summary statistics, we estimated the liability-scale SNP-based heritability of ALS to be 8.2% (95% confidence interval = 7.2–9.1; mean $\chi^2 = 1.13$; all ranges reported below indicate 95% confidence intervals), replicating previous estimates based on alternative methods⁷. Estimates based on ALS meta-analysis summary statistics and free-intercept LD score regression with mixed linear model summary statistics were lower (Supplementary Table 1), resulting in higher genetic correlation estimates (Supplementary Table 2); for this reason, we conservatively use constrained intercept genetic correlation estimates for ALS mixed linear model summary statistics throughout the remainder of this paper. Heritability estimates for permuted ALS data were null (Supplementary Table 1).

LD score regression estimated the genetic correlation between ALS and schizophrenia to be 14.3% (7.05–21.6; $P = 1 \times 10^{-4}$). Results were similar for a smaller schizophrenia cohort of European ancestry (21,856 individuals)¹⁴, indicating that the inclusion of individuals of Asian ancestry in the schizophrenia cohort did not bias this result (Supplementary Fig. 1). In addition to schizophrenia, we estimated genetic correlation with ALS using GWAS summary statistics for bipolar disorder¹⁵, major depressive disorder¹⁶, attention deficit-hyperactivity disorder¹⁷, autism spectrum disorder¹⁷, Alzheimer's disease (Supplementary Note 1)¹⁸, multiple sclerosis¹⁹ and adult height²⁰, finding no significant genetic correlation between ALS and any secondary trait other than schizophrenia (Fig. 1; Supplementary Table 2).

Polygenic risk score analysis. We supported the positive genetic correlation between ALS and schizophrenia by analysis of

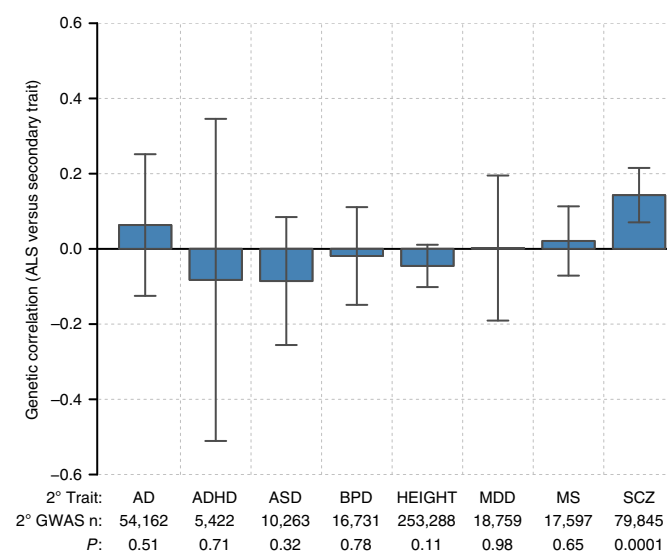


Figure 1 | Genetic correlation between ALS and eight secondary traits.

Error bars indicating 95% confidence intervals and P -values were calculated by the LD score regression software using a block jackknife procedure. Secondary traits are: AD, Alzheimer's disease; ADHD, attention deficit-hyperactivity disorder; ASD, autism spectrum disorder; BPD, bipolar disorder; MDD, major depressive disorder; MS, multiple sclerosis; SCZ, schizophrenia.

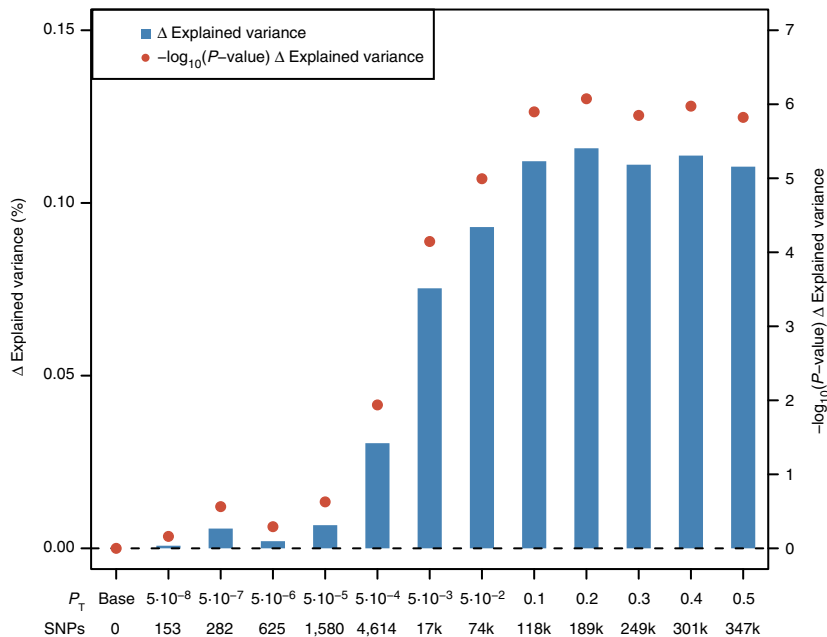


Figure 2 | Analysis of PRS for schizophrenia in a target sample of 10,032 ALS cases and 16,627 healthy controls. P -value thresholds (P_T) for schizophrenia SNPs are shown on the x axis, where the number of SNPs increases with a more lenient P_T . Δ Explained variances (Nagelkerke R^2 , shown as a %) of a generalized linear model including schizophrenia-based PRS versus a baseline model without polygenic scores (blue bars) are shown for each P_T . $-\log_{10} P$ -values of Δ explained variance per P_T (red dots) represent P -values from the binomial logistic regression of ALS phenotype on PRS, accounting for LD (Supplementary Table 4) and including sex and significant principal components as covariates (Supplementary Fig. 2). Values are provided in Supplementary Table 5.

polygenic risk for schizophrenia in the ALS cohort. Polygenic risk scores (PRS) are per-individual scores based on the sum of alleles associated with one phenotype, weighted by their effect size, measured in an independent target sample of the same or a different phenotype¹⁰. PRS calculated on schizophrenia GWAS summary statistics for twelve P -value thresholds (P_T) explained up to 0.12% ($P_T=0.2$, $P=8.4 \times 10^{-7}$) of the phenotypic variance in a subset of the individual-level ALS genotype data that had all individuals removed that were known or suspected to be present in the schizophrenia cohort (Fig. 2; Supplementary Table 5). ALS cases had on average higher PRS for schizophrenia compared to healthy controls and harbouring a high schizophrenia PRS for $P_T=0.2$ significantly increased the odds of being an ALS patient in our cohort (Fig. 3; Supplementary Table 6). Permutation of case-control labels reduced the explained variance to values near zero (Supplementary Fig. 3).

Modelling misdiagnosis and comorbidity. Using BUHMBBOX²¹, a tool that distinguishes true genetic relationships between diseases (pleiotropy) from spurious relationships resulting from heterogeneous mixing of disease cohorts, we determined that misdiagnosed cases in the schizophrenia cohort (for example, young-onset FTD-ALS) did not drive the genetic correlation estimate between ALS and schizophrenia ($P=0.94$). Assuming a true genetic correlation of 0%, we estimated the required rate of misdiagnosis of ALS as schizophrenia to be 4.86% (2.47–7.13) to obtain the genetic correlation estimate of 14.3% (7.05–21.6; Supplementary Table 7), which we consider to be too high to be likely. However, if ALS and schizophrenia are genetically correlated, more comorbidity would be expected than if the genetic correlation was 0%. Modelling our observed genetic correlation of 14.3% (7.05–21.6), we estimated the odds ratio for having above-threshold liability for ALS given above-threshold liability for schizophrenia to be 1.17 (1.08–1.26), and the same for schizophrenia given ALS (Supplementary Fig. 4). From a clinical

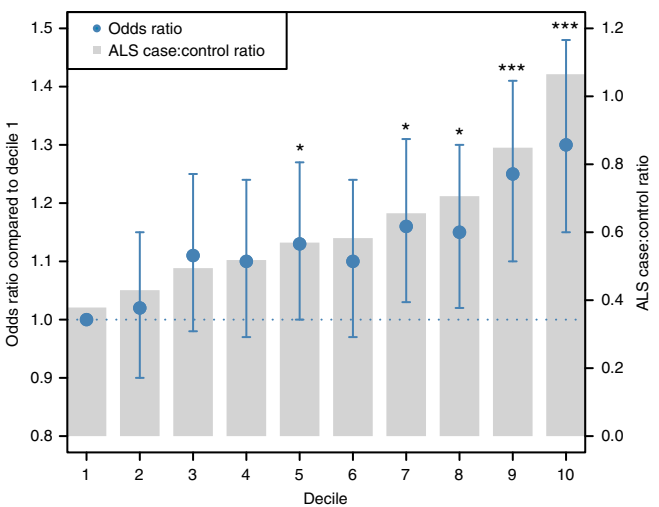


Figure 3 | Odds ratio for ALS by PRS deciles for schizophrenia. The figure applies to schizophrenia P -value threshold (P_T) = 0.2. The PRS for this threshold were converted to ten deciles containing near identical numbers of individuals. Decile 1 contained the lowest scores and decile 10 contained the highest scores, where decile 1 was the reference and deciles 2–10 were dummy variables to contrast to decile 1 for OR calculation. The case:control ratio per decile is indicated with grey bars. Error bars indicate 95% confidence intervals. Significant differences from decile 1 were determined by logistic regression of ALS phenotype on PRS decile, including sex and principal components as covariates and are indicated by * $P<0.05$ or *** $P<0.001$.

perspective, to achieve 80% power to detect a significant ($\alpha=0.05$) excess of schizophrenia in the ALS cohort as a result of this genetic correlation, the required population-based incident cohort size is 16,448 ALS patients (7,310–66,670).

Pleiotropic risk loci. We leveraged the genetic correlation between ALS and schizophrenia to discover novel ALS-associated genomic loci by conditional false discovery rate (cFDR) analysis^{9,22} (Fig. 4; Supplementary Table 8). Five loci already known to be involved in ALS were identified (corresponding to *MOBP*, *C9orf72*, *TBK1*, *SARM1* and *UNC13A*) along with five potential novel loci at $cFDR < 0.01$ (*CNTN6*, *TNIP1*, *PPP2R2D*, *NCKAP5L* and *ZNF295-AS1*). No gene set was significantly enriched (after Bonferroni correction) in genome-wide cFDR values when analysed using MAGENTA.

Discussion

There is evolving clinical, epidemiological and biological evidence for an association between ALS and psychotic illness, particularly schizophrenia. Genetic evidence of overlap to date has been based primarily on individual genes showing Mendelian inheritance, in particular the *C9orf72* hexanucleotide repeat expansion, which is associated with ALS and FTD, and with psychosis in relatives of ALS patients². In this study, we have replicated SNP-based heritability estimates for ALS and schizophrenia using GWAS summary statistics, and have for the first time demonstrated significant overlap between the polygenic components of both diseases, estimating the genetic correlation to be 14.3%. We have carefully controlled for confounding bias, including population stratification and shared control samples, and have shown through analysis of polygenic risk scores that the overlapping polygenic risk applies to SNPs that are modestly associated with both diseases. Given that our genetic correlation estimate relates to the polygenic components of ALS ($h^2_S = 8.2\%$) and schizophrenia ($h^2_S = 23\%$) and these estimates do not represent all heritability for both diseases, the accuracy of using schizophrenia-based PRS to predict ALS status in any patient is expected to be low (Nagelkerke's $R^2 = 0.12\%$ for $P_T = 0.2$), although statistically significant ($P = 8.4 \times 10^{-7}$). Nevertheless, the positive genetic correlation of 14.3% indicates that the direction of effect of risk-increasing and protective alleles is consistently aligned between ALS and schizophrenia, suggesting convergent biological mechanisms between the two diseases.

Although phenotypically heterogeneous, both ALS and schizophrenia are clinically recognizable as syndromes^{23,24}. The common biological mechanisms underlying the association between the two conditions are not well understood, but are likely associated with disruption of cortical networks. Schizophrenia is a

polygenic neurodevelopmental disorder characterized by a combination of positive symptoms (hallucinations and delusions), negative symptoms (diminished motivation, blunted affect, reduction in spontaneous speech and poor social functioning) and impairment over a broad range of cognitive abilities²⁵. ALS is a late onset complex genetic disease characterized by a predominantly motor phenotype with recently recognized extra-motor features in 50% of patients, including cognitive impairment¹. It has been suggested that the functional effects of risk genes in schizophrenia converge by modulating synaptic plasticity, and influencing the development and stabilization of cortical microcircuitry⁵. In this context, our identification of *CNTN6* (contactin 6, also known as NB-3, a neural adhesion protein important in axon development)²⁶ as a novel pleiotropy-informed ALS-associated locus supports neural network dysregulation as a potential convergent mechanism of disease in ALS and schizophrenia.

No significantly enriched biological pathway or ontological term was identified within genome-wide cFDR values using MAGENTA. Low inflation in ALS GWAS statistics, coupled with a rare variant genetic architecture⁷, render enrichment-based biological pathway analyses with current sample sizes challenging. Nevertheless, nine further loci were associated with ALS risk at $cFDR < 0.01$. Of these, *MOBP*, *C9orf72*, *TBK1*, *SARM1* and *UNC13A* have been described previously in ALS and were associated by cFDR analysis in this study owing to their strong association with ALS through GWAS⁷. The remaining four loci (*TNIP1*, *PPP2R2D*, *NCKAP5L* and *ZNF295-AS1*) are novel associations and may represent pleiotropic disease loci. *TNIP1* encodes TNFAIP3 interacting protein 1 and is involved in autoimmunity and tissue homeostasis²⁷. The protein product of *PPP2R2D* is a regulatory subunit of protein phosphatase 2 and has a role in PI3K-Akt signalling and mitosis²⁸. *NCKAP5L* is a homologue of *NCKAP5*, encoding NAP5, a proline-rich protein that has previously been implicated in schizophrenia, bipolar disorder and autism^{29,30}. *ZNF295-AS1* is a noncoding RNA³¹. Further investigation into the biological roles of these genes may yield novel insight into the pathophysiology of certain subtypes of ALS and schizophrenia, and as whole-genome and exome datasets become available in the future for appropriately large ALS case-control cohorts, testing for burden of rare genetic variation across these genes will be particularly instructive, especially given the role that rare variants appear to play in the pathophysiology of ALS⁷.

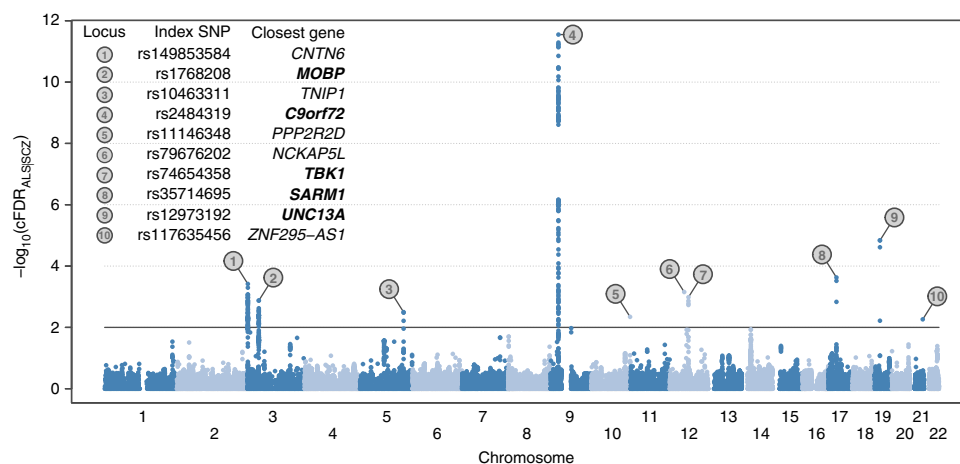


Figure 4 | Pleiotropy-informed ALS risk loci determined by analysis of cFDR in ALS GWAS P-values given schizophrenia GWAS P-values

($cFDR_{ALS|SCZ}$). Each point denotes a SNP; its x axis position corresponds to its chromosomal location and its height indicates the extent of association with ALS by cFDR analysis. The solid line indicates the threshold $cFDR = 0.01$. Any gene whose role in ALS is already established is in bold. A complete list of all loci at $cFDR \leq 0.05$ is provided in Supplementary Table 8.

Our data suggest that other neuropsychiatric conditions (bipolar disorder, autism and major depression) do not share polygenic risk with ALS. This finding contrasts with our recent observations from family aggregation studies and may be unexpected given the extensive genetic correlation between neuropsychiatric conditions⁶. This could relate to statistical power conferred by secondary phenotype cohort sizes, and future studies with larger sample sizes will shed further light on the relationship between ALS and neuropsychiatric disease. It is also possible that the current study underestimates genetic correlations due to the substantial role that rare variants play in the genetic architecture of ALS⁷ and future fine-grained studies examining heritability and genetic correlation in low-minor allele frequency and low-LD regions may identify a broader relationship between ALS and neuropsychiatric diseases.

A potential criticism of this study is that the polygenic overlap between ALS and schizophrenia could be driven by misdiagnosis, particularly in cases of ALS-FTD, which can present in later life as a psychotic illness and could be misdiagnosed as schizophrenia. This is unlikely, as strict diagnostic criteria are required for inclusion of samples in the schizophrenia GWAS dataset⁵. Furthermore, since core schizophrenia symptoms are usually diagnosed during late adolescence, a misdiagnosis of FTD-onset ALS-FTD as schizophrenia is unlikely. In this study, we found no evidence for misdiagnosis of ALS as schizophrenia (BUHMBOX $P=0.94$) and we estimated that a misdiagnosis of 4.86% of ALS cases would be required to spuriously observe a genetic correlation of 14.3%, which is not likely to occur in clinical practice. We are therefore confident that this genetic correlation estimate reflects a genuine polygenic overlap between the two diseases and is not a feature of cohort ascertainment, but the possibility of some misdiagnosis in either cohort cannot be entirely excluded based on available data.

A positive genetic correlation between ALS and schizophrenia predicts an excess of patients presenting with both diseases. Most neurologists and psychiatrists, however, will not readily acknowledge that these conditions co-occur frequently. Our genetic correlation estimate confers an odds ratio of 1.17 (1.08–1.26) for harbouring above-threshold liability for ALS given schizophrenia (or vice versa) and a lifetime risk of 1:34,336 for both phenotypes together. Thus, a very large incident cohort of 16,448 ALS patients (7,310–66,670), with detailed phenotype information, would be required to have sufficient power to detect an excess of schizophrenia within an ALS cohort. Coupled with reduced life expectancy in patients with schizophrenia³², this may explain the relative dearth of epidemiological studies to date providing clinical evidence of excess comorbidity. Moreover, it has also been proposed that prolonged use of antipsychotic medication may protect against developing all of the clinical features of ALS³³, which would reduce the rate of observed comorbidity. Considering our novel evidence for a genetic relationship between ALS and schizophrenia, this underscores the intriguing possibility that therapeutic strategies for each condition may be useful in the other, and our findings provide rationale to consider the biology of ALS and schizophrenia as related in future drug development studies. Indeed, the glutamate-modulating ALS therapy riluzole has shown efficacy as an adjunct to risperidone, an antipsychotic medication, in reducing the negative symptoms of schizophrenia³⁴.

In conclusion, we have estimated the genetic correlation between ALS and schizophrenia to be 14.3% (7.05–21.6), providing molecular genetic support for our epidemiological observation of psychiatric endophenotypes within ALS kindreds. To our knowledge, this is the first study to show genetic correlation derived from polygenic overlap between neurodegenerative and neuropsychiatric phenotypes. The presence of

both apparent monogenic *C9orf72*-driven overlap² and polygenic overlap in the aetiology of ALS and schizophrenia suggests the presence of common biological processes, which may relate to disruption of cortical circuitry. As both ALS and schizophrenia are heterogeneous conditions, further genomic, biological and clinical studies are likely to yield novel insights into the pathological processes for both diseases and will provide clinical sub-stratification parameters that could drive novel drug development for both neurodegenerative and psychiatric conditions.

Methods

Study population and genetic data. For ALS, 7,740,343 SNPs genotyped in 12,577 ALS patients and 23,475 healthy controls of European ancestry organized in 27 platform- and country-defined strata were used⁷. The schizophrenia dataset comprised GWAS summary statistics for 9,444,230 SNPs originally genotyped in 34,241 patients and 45,604 controls of European and Asian ancestry⁵. For LD score regression, GWAS summary statistics were generated for the ALS cohort using mixed linear model association testing implemented in Genome-wide Complex Trait Analysis¹¹ or logistic regression combined with cross-stratum meta-analysis using METAL¹². To evaluate sample overlap for PRS and cFDR analyses, we also obtained individual-level genotype data for 27,647 schizophrenia cases and 33,675 controls from the schizophrenia GWAS (Psychiatric Genomics Consortium⁵ and dbGaP accession number phs000021.v3.p2). Using 88,971 LD-pruned (window size 200 SNPs; shift 20 SNPs; $r^2 > 0.25$) SNPs in both datasets (INFO score > 0.8 ; MAF > 0.2), with SNPs in high-LD regions removed (Supplementary Table 4), samples were removed from the ALS dataset if they were duplicated or had a cryptically related counterpart (PLINK $\pi > 0.1$; 5,582 individuals) in the schizophrenia cohort and whole strata (representing Finnish and German samples; 3,811 individuals) were also removed if commonality with the schizophrenia cohort could not be ascertained (due to unavailability of individual-level genotype data in the schizophrenia cohort) and in which a sample overlap was suspected (Supplementary Table 3).

LD score regression. We calculated LD scores using LDSC v1.0.0 in 1 centiMorgan windows around 13,307,412 non-singleton variants genotyped in 379 European individuals (CEU, FIN, GBR, IBS and TSI populations) in the phase 1 integrated release of the 1,000 Genomes Project³⁵. For regression weights¹³, we restricted LD score calculation to SNPs included in both the GWAS summary statistics and HapMap phase 3; for r_g estimation in pairs of traits this was the intersection of SNPs for both traits and HapMap. Because population structure and confounding were highly controlled in the ALS summary statistics by the use of mixed linear model association tests, we constrained the LD score regression intercept to 1 for h_g^2 estimation in ALS, and we also estimated h_g^2 with a free intercept. For h_g^2 estimation in all other traits and for r_g estimation the intercept was a free parameter. We also estimated r_g using ALS meta-analysis results⁷ with free and constrained intercepts and with permuted data conserving population structure. Briefly, principal component analysis was carried out for each stratum using smartpca³⁶ and the three-dimensional space defined by principal components 1–3 was equally subdivided into 1,000 cubes. Within each cube, case-control labels were randomly swapped and association statistics were re-calculated for the entire stratum using logistic regression. Study-level P -values were then calculated using inverse variance weighted fixed effect meta-analysis implemented in METAL^{7,12}. h_g^2 was estimated for these meta-analysed permuted data using LD score regression (Supplementary Table 1).

Polygenic risk score analysis. We calculated PRS for 10,032 cases and 16,627 healthy controls in the ALS dataset (duplicate and suspected or confirmed related samples with the schizophrenia dataset removed), based on schizophrenia-associated alleles and effect sizes reported in the GWAS summary statistics for 6,843,674 SNPs included in both studies and in the phase 1 integrated release of the 1,000 Genomes Project³⁵ (imputation INFO score < 0.3 ; minor allele frequency < 0.01 ; A/T and G/C SNPs removed). SNPs were clumped in two rounds (physical distance threshold of 250 kb and a LD threshold (R^2) of > 0.5 in the first round and a distance of 5,000 kb and LD threshold of > 0.2 in the second round) using PLINK v1.90b3y, removing high-LD regions (Supplementary Table 4), resulting in a final set of 496,548 SNPs for PRS calculations. Odds ratios for autosomal SNPs reported in the schizophrenia summary statistics were log-converted to beta values and PRS were calculated using PLINK's score function for twelve schizophrenia GWAS P -value thresholds (P_T): 5×10^{-8} , 5×10^{-7} , 5×10^{-6} , 5×10^{-5} , 5×10^{-4} , 5×10^{-3} , 0.05, 0.1, 0.2, 0.3, 0.4 and 0.5. A total of 100 principal components (PCs) were generated for the ALS sample using GCTA version 1.24.4. Using R version 3.2.2, a generalized linear model was applied to model the phenotype of individuals in the ALS dataset. PCs that had a significant effect on the phenotype ($P < 0.0005$, Bonferroni-corrected for 100 PCs) were selected (PCs 1, 4, 5, 7, 8, 10, 11, 12, 14, 36, 49).

To estimate explained variance of PRS on the phenotype, a baseline linear relationship including only sex and significant PCs as variables was modelled first:

$$y = \alpha + \beta_{\text{sex}} x_{\text{sex}} + \sum_n \beta_{\text{PC}_n} x_{\text{PC}_n},$$

where y is the phenotype in the ALS dataset, α is the intercept of the model with a slope β for each variable x .

Subsequently, a linear model including polygenic scores for each schizophrenia P_T was calculated:

$$y = \alpha + \beta_{\text{sex}} x_{\text{sex}} + \sum_n \beta_{\text{PC}_n} x_{\text{PC}_n} + \beta_{\text{PRS}} x_{\text{PRS}}.$$

A Nagelkerke R^2 value was obtained for every model and the baseline Nagelkerke R^2 value was subtracted, resulting in a Δ explained variance that describes the contribution of schizophrenia-based PRS to the phenotype in the ALS dataset. PRS analysis was also performed in permuted case-control data (1,000 permutations, conserving case-control ratio) to assess whether the increased Δ explained variance was a true signal associated with phenotype. Δ explained variances and P -values were averaged across permutation analyses.

To ensure we did not over- or under-correct for population effects in our model, we tested the inclusion of up to a total of 30 PCs in the model, starting with the PC with the most significant effect on the ALS phenotype (Supplementary Fig. 2). Increasing the number of PCs initially had a large effect on the Δ explained variance, but this effect levelled out after 11 PCs. On the basis of this test we are confident that adding the 11 PCs that had a significant effect on the phenotype sufficiently accounted for possible confounding due to population differences.

For the schizophrenia P_T for which we obtained the highest Δ explained variance (0.2), we subdivided observed schizophrenia-based PRS in the ALS cohort into deciles and calculated the odds ratio for being an ALS case in each decile compared to the first decile using a similar generalized linear model:

$$y = \alpha + \beta_{\text{sex}} x_{\text{sex}} + \sum_n \beta_{\text{PC}_n} x_{\text{PC}_n} + \beta_{\text{decile}} x_{\text{decile}}.$$

Odds ratios and 95% confidence intervals for ALS were derived by calculating the exponential function of the beta estimate of the model for each of the deciles 2–10.

Diagnostic misclassification. To distinguish the contribution of misdiagnosis from true genetic pleiotropy we used BUHMBOX²¹ with 417 independent ALS risk alleles in a sample of 27,647 schizophrenia patients for which individual-level genotype data were available. We also estimated the required misdiagnosis rate M of FTD-ALS as schizophrenia that would lead to the observed genetic correlation estimate as $C/(C+1)$, where $C = \rho_{\text{NSCZ}/N_{\text{ALS}}}$ and N_{SCZ} and N_{ALS} are the number of cases in the schizophrenia and ALS datasets, respectively³⁷ (derived in Supplementary Methods 1).

Expected comorbidity. To investigate the expected comorbidity of ALS and schizophrenia given the observed genetic correlation, we modelled the distribution in liability for ALS and schizophrenia as a bivariate normal distribution with the liability-scale covariance determined by LD score regression (Supplementary Methods 2). Lifetime risks for ALS³⁸ and schizophrenia²⁵ of 1/400 and 1/100, respectively, were used to calculate liability thresholds above which individuals develop ALS or schizophrenia, or both. The expected proportions of individuals above these thresholds were used to calculate the odds ratio of developing ALS given schizophrenia, or vice versa (Supplementary Methods 2). The required population size to observe a significant excess of comorbidity was calculated using the binomial power equation.

Pleiotropy-informed risk loci for ALS. Using an adapted cFDR method⁹ that allows shared controls between cohorts²², we estimated per-SNP cFDR given LD score-corrected⁸ schizophrenia GWAS P -values for ALS mixed linear model summary statistics calculated in a dataset excluding Finnish and German cohorts (in which suspected control overlap could not be determined), but including all other overlapping samples (totalling 5,582). To correct for the relationship between LD and GWAS test statistics, schizophrenia summary statistics were residualized on LD score by subtracting the product of each SNP's LD score and the univariate LD score regression coefficient for schizophrenia. cFDR values conditioned on these residualized schizophrenia GWAS P -values were calculated for mixed linear model association statistics calculated at 6,843,670 SNPs genotyped in 10,147 ALS cases and 22,094 controls. Pleiotropic genomic loci were considered statistically significant if cFDR < 0.01 (following Andreassen *et al.*⁹) and were clumped with all neighbouring SNPs based on LD ($r^2 > 0.1$) in the complete ALS dataset. Associated cFDR genomic regions were then mapped to the locations of known RefSeq transcripts in human genome build GRCh37. Genome-wide cFDR values were also tested for enrichment in 9,711 gene sets included in the MAGENTA software package (version 2.4, July 2011) and derived from databases such as Gene Ontology (GO, <http://geneontology.org/>), Kyoto Encyclopedia of Genes and Genomes (KEGG, <http://www.kegg.jp/>), Protein ANalysis THrough Evolutionary Relationships (PANTHER, <http://www.pantherdb.org/>) and INGENUITY (<http://www.ingenuity.com/>). SNPs were mapped to genes including 20 kb up- and downstream regions to include regulatory elements. The enrichment cutoff applied

in our analysis was based on the 95th percentile of gene scores for all genes in the genome. The null distribution of gene scores for each gene set was based on 10,000 randomly sampled gene sets with equal size. MAGENTA uses a Mann-Whitney rank-sum test to assess gene-set enrichment³⁹.

Data availability. All data used in this study are publically available and can be accessed via the studies cited in the text. Other data are available from the authors upon reasonable request.

References

- Phukan, J. *et al.* The syndrome of cognitive impairment in amyotrophic lateral sclerosis: a population-based study. *J. Neurol. Neurosurg. Psychiatry* **83**, 102–108 (2012).
- Byrne, S. *et al.* Aggregation of neurologic and neuropsychiatric disease in amyotrophic lateral sclerosis kindreds: a population-based case-control cohort study of familial and sporadic amyotrophic lateral sclerosis. *Ann. Neurol.* **74**, 699–708 (2013).
- Al-Chalabi, A. *et al.* An estimate of amyotrophic lateral sclerosis heritability using twin data. *J. Neurol. Neurosurg. Psychiatry* **81**, 1324–1326 (2010).
- Lichtenstein, P. *et al.* Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. *Lancet Lond. Engl* **373**, 234–239 (2009).
- Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. *Nature* **511**, 421–427 (2014).
- Cross-Disorder Group of the Psychiatric Genomics Consortium. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nat. Genet.* **45**, 984–994 (2013).
- van Rheenen, W. *et al.* Genome-wide association analyses identify new risk variants and the genetic architecture of amyotrophic lateral sclerosis. *Nat. Genet.* **48**, 1043–1048 (2016).
- Bulik-Sullivan, B. *et al.* An atlas of genetic correlations across human diseases and traits. *Nat. Genet.* **47**, 1236–1241 (2015).
- Andreassen, O. A. *et al.* Improved detection of common variants associated with schizophrenia by leveraging pleiotropy with cardiovascular-disease risk factors. *Am. J. Hum. Genet.* **92**, 197–209 (2013).
- International Schizophrenia Consortium. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature* **460**, 748–752 (2009).
- Yang, J., Zaitlen, N. A., Goddard, M. E., Visscher, P. M. & Price, A. L. Advantages and pitfalls in the application of mixed-model association methods. *Nat. Genet.* **46**, 100–106 (2014).
- Willer, C. J., Li, Y. & Abecasis, G. R. METAL: fast and efficient meta-analysis of genomewide association scans. *Bioinformatics* **26**, 2190–2191 (2010).
- Bulik-Sullivan, B. K. *et al.* LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat. Genet.* **47**, 291–295 (2015).
- Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium. Genome-wide association study identifies five new schizophrenia loci. *Nat. Genet.* **43**, 969–976 (2011).
- Psychiatric GWAS Consortium Bipolar Disorder Working Group. Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. *Nat. Genet.* **43**, 977–983 (2011).
- Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium. A mega-analysis of genome-wide association studies for major depressive disorder. *Mol. Psychiatry* **18**, 497–511 (2013).
- Cross-Disorder Group of the Psychiatric Genomics Consortium. Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. *Lancet Lond. Engl.* **381**, 1371–1379 (2013).
- Lambert, J. C. *et al.* Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. *Nat. Genet.* **45**, 1452–1458 (2013).
- Patsopoulos, N. A. *et al.* Genome-wide meta-analysis identifies novel multiple sclerosis susceptibility loci. *Ann. Neurol.* **70**, 897–912 (2011).
- Wood, A. R. *et al.* Defining the role of common variation in the genomic and biological architecture of adult human height. *Nat. Genet.* **46**, 1173–1186 (2014).
- Han, B. *et al.* A method to decipher pleiotropy by detecting underlying heterogeneity driven by hidden subgroups applied to autoimmune and neuropsychiatric diseases. *Nat. Genet.* **48**, 803–810 (2016).
- Liley, J. & Wallace, C. A pleiotropy-informed Bayesian false discovery rate adapted to a shared control design finds new disease associations from GWAS summary statistics. *PLoS Genet.* **11**, e1004926 (2015).
- Brown, A. S. & McGrath, J. J. The prevention of schizophrenia. *Schizophr. Bull.* **37**, 257–261 (2011).
- Al-Chalabi, A. *et al.* Amyotrophic lateral sclerosis: moving towards a new classification system. *Lancet Neurol.* **15**, 1182–1194 (2016).
- Kahn, R. S. *et al.* Schizophrenia. *Nat. Rev. Dis. Primer* **1**, 15067 (2015).

26. Huang, Z., Yu, Y., Shimoda, Y., Watanabe, K. & Liu, Y. Loss of neural recognition molecule NB-3 delays the normal projection and terminal branching of developing corticospinal tract axons in the mouse. *J. Comp. Neurol.* **520**, 1227–1245 (2012).
27. Ramirez, V. P., Gurevich, I. & Aneskievich, B. J. Emerging roles for TNIP1 in regulating post-receptor signaling. *Cytokine Growth Factor Rev.* **23**, 109–118 (2012).
28. Toker, A. & Marmiroli, S. Signaling specificity in the Akt pathway in biology and disease. *Adv. Biol. Regul.* **55**, 28–38 (2014).
29. Wang, K.-S., Liu, X.-F. & Aragam, N. A genome-wide meta-analysis identifies novel loci associated with schizophrenia and bipolar disorder. *Schizophr. Res.* **124**, 192–199 (2010).
30. Chahrouh, M. H. *et al.* Whole-exome sequencing and homozygosity analysis implicate depolarization-regulated neuronal genes in autism. *PLoS Genet.* **8**, e1002635 (2012).
31. Ota, T. *et al.* Complete sequencing and characterization of 21,243 full-length human cDNAs. *Nat. Genet.* **36**, 40–45 (2004).
32. Laursen, T. M., Munk-Olsen, T. & Vestergaard, M. Life expectancy and cardiovascular mortality in persons with schizophrenia. *Curr. Opin. Psychiatry* **25**, 83–88 (2012).
33. Stommel, E. W., Graber, D., Montanye, J., Cohen, J. A. & Harris, B. T. Does treating schizophrenia reduce the chances of developing amyotrophic lateral sclerosis? *Med. Hypotheses* **69**, 1021–1028 (2007).
34. Farokhnia, M. *et al.* A double-blind, placebo controlled, randomized trial of riluzole as an adjunct to risperidone for treatment of negative symptoms in patients with chronic schizophrenia. *Psychopharmacology* **231**, 533–542 (2014).
35. McVean, G. A. *et al.* An integrated map of genetic variation from 1,092 human genomes. *Nature* **491**, 56–65 (2012).
36. Patterson, N., Price, A. L. & Reich, D. Population structure and eigenanalysis. *PLoS Genet.* **2**, e190 (2006).
37. Wray, N. R., Lee, S. H. & Kendler, K. S. Impact of diagnostic misclassification on estimation of genetic correlations using genome-wide genotypes. *Eur. J. Hum. Genet.* **20**, 668–674 (2012).
38. Johnston, C. A. *et al.* Amyotrophic lateral sclerosis in an urban setting: a population based study of inner city London. *J. Neurol.* **253**, 1642–1643 (2006).
39. Segrè, A. V. *et al.* Common inherited variation in mitochondrial genes is not enriched for associations with type 2 diabetes or related glycemic traits. *PLoS Genet.* **6**, e1001058 (2010).

Acknowledgements

We acknowledge helpful contributions from Mr Gert Jan van de Vendel in the design and execution of PRS analyses. This study received support from the ALS Association; Fondation Thierry Latran; the Motor Neurone Disease Association of England, Wales and Northern Ireland; Science Foundation Ireland; Health Research Board (Ireland), The Netherlands ALS Foundation (Project MinE, to J.H.V., L.H.v.d.B.), the Netherlands Organisation for Health Research and Development (Vici scheme, L.H.v.d.B.) and ZonMW under the frame of E-Rare-2, the ERA Net for Research on Rare Diseases (PYRAMID). Research leading to these results has received funding from the European Community's Health Seventh Framework Programme (FP7/2007–2013). A.G. is supported by the Research Foundation KU Leuven (C24/16/045). A.A.-C. received salary support from the National Institute for Health Research (NIHR) Dementia Biomedical Research Unit and Biomedical Research Centre in Mental Health at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. Samples used in this research were in part obtained from the UK National DNA Bank for MND Research, funded by the MND Association and the Wellcome Trust. We acknowledge sample management undertaken by Biobanking Solutions funded by the Medical Research Council (MRC) at the Centre for Integrated Genomic Medical Research, University of Manchester. This is an EU Joint Programme-Neuro-degenerative Disease Research (JPND) Project (STRENGTH, SOPHIA). In addition to those mentioned above, the project is supported through the following funding organizations under the aegis of JPND: UK, Economic and Social Research Council; Italy, Ministry of Health and Ministry of Education, University and Research; France, L'Agence nationale pour la recherche. The work leading up to this publication was funded by the European Community's Health Seventh Framework Programme (FP7/2007–2013; Grant Agreement Number 2,59,867). We thank the International Genomics of Alzheimer's Project (IGAP) for providing summary results data for these

analyses. The investigators within IGAP provided data but did not participate in analysis or writing of this report. IGAP was made possible by the generous participation of the control subjects, the patients, and their families. The i-Select chips was funded by the French National Foundation on Alzheimer's disease and related disorders. EADI was supported by the LABEX (laboratory of excellence program investment for the future) DISTALZ grant, Inserm, Institut Pasteur de Lille, Université de Lille 2 and the Lille University Hospital. GERAD was supported by the MRC (Grant No. 5,03,480), Alzheimer's Research UK (Grant No. 5,03,176), the Wellcome Trust (Grant No. 082604/2/07/Z) and German Federal Ministry of Education and Research: Competence Network Dementia Grant no. 01GI0102, 01GI0711, 01GI0420. CHARGE was partly supported by the NIH/NIA Grant R01 AG033193 and the NIA AG081220 and AGES contract N01-AG-12,100, the NHLBI Grant R01 HL105756, the Icelandic Heart Association, and the Erasmus Medical Center and Erasmus University. ADGC was supported by the NIH/NIA Grants: U01 AG032984, U24 AG021886, U01 AG016976, and the Alzheimer's Association Grant ADGC-10-196728. The Project MinE GWAS Consortium included contributions from the PARALS registry, SLALOM group, SLAP registry, FALS Sequencing Consortium, SLAGEN Consortium and NNIPPS Study Group; the Schizophrenia Working Group of the Psychiatric Genomics Consortium included contributions from the Psychosis Endophenotypes International Consortium and Wellcome Trust Case-control Consortium. Members of these eight consortia are listed in Supplementary Note 2.

Author contributions

O.H., J.H.V. and A.A.-C. conceived the study. R.L.McL., D.S., W.v.R., K.R.v.E., M.O'B., D.G.B., A.A.-C., L.H.v.d.B., J.J.L., O.H. and J.H.V. contributed to study design. R.L.McL., D.S. and W.v.R. conducted the analyses. R.L.McL., D.S., O.H., J.J.L. and J.H.V. drafted the manuscript. R.S.K., R.A.O. and A.G. provided data and critical revision of the manuscript. The Project MinE GWAS Consortium and Schizophrenia Working Group of the Psychiatric Genomics Consortium provided data. R.L.McL. and D.S. contributed equally. J.J.L., O.H. and J.H.V. jointly directed the work.

Additional information

Supplementary Information accompanies this paper at <http://www.nature.com/naturecommunications>

Competing interests: O.H. has received speaking honoraria from Novartis, Biogen Idec, Sanofi Aventis and Merck-Serono. She has been a member of advisory panels for Biogen Idec, Allergan, Ono Pharmaceuticals, Novartis, Cytokinetics and Sanofi Aventis. She serves as Editor-in-Chief of Amyotrophic Lateral Sclerosis and Frontotemporal Dementia. L.H.v.d.B. serves on scientific advisory boards for Prinses Beatrix Spierfonds, Thierry Latran Foundation, Baxalta, Cytokinetics and Biogen, serves on the Editorial Board of the Journal of Neurology, Neurosurgery, and Psychiatry, Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, and Journal of Neuromuscular Diseases. A.A.C. has served on advisory panels for Biogen Idec, Cytokinetics, GSK, OrionPharma and Mitsubishi-Tanabe, serves on the Editorial Boards of Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration and F1000, and receives royalties for The Brain: A Beginner's Guide, OneWorld Publications, and Genetics of Complex Human Diseases, Cold Spring Harbor Laboratory Press. The remaining authors declare no competing financial interests.

Reprints and permission information is available online at <http://npg.nature.com/reprintsandpermissions/>

How to cite this article: McLaughlin, R. L. *et al.* Genetic correlation between amyotrophic lateral sclerosis and schizophrenia. *Nat. Commun.* **8**, 14774 doi: 10.1038/ncomms14774 (2017).

Publisher's note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.



This work is licensed under a Creative Commons Attribution 4.0 International License. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in the credit line; if the material is not included under the Creative Commons license, users will need to obtain permission from the license holder to reproduce the material. To view a copy of this license, visit <http://creativecommons.org/licenses/by/4.0/>

© The Author(s) 2017

Project MinE GWAS Consortium

Aleksey Shatunov⁸, Annelot M. Dekker³, Frank P. Diekstra³, Sara L. Pulit⁴, Rick A.A. van der Spek³, Perry T.C. van Doormaal³, William Sproviero⁸, Ashley R. Jones⁸, Garth A. Nicholson^{10,11}, Dominic B. Rowe¹⁰, Roger Pamphlett¹², Matthew C. Kiernan¹³, Denis Bauer¹⁴, Tim Kahlke¹⁴, Kelly Williams¹⁰, Filip Eftimov¹⁵, Isabella Fogh^{8,16}, Nicola Ticozzi^{16,17}, Kuang Lin⁸, Stéphanie Millecamps¹⁸, François Salachas¹⁹, Vincent Meininger¹⁹, Mamede de Carvalho^{20,21}, Susana Pinto^{20,21}, Jesus S. Mora²², Ricardo Rojas-García²³, Meraida Polak²⁴, Siddharthan Chandran^{25,26}, Shuna Colville²⁵, Robert Swingle²⁵, Karen E. Morrison^{27,28}, Pamela J. Shaw²⁹, John Hardy³⁰, Richard W. Orrell³¹, Alan Pittman^{30,32}, Katie Sidle³¹, Pietro Fratta³³, Andrea Malaspina^{34,35}, Susanne Petri³⁶, Susanna Abdulla³⁷, Carsten Drepper³⁸, Michael Sendtner³⁸, Thomas Meyer³⁹, Martina Wiedau-Pazos⁵, Catherine Lomen-Hoerth⁴⁰, Vivianne M. Van Deerlin⁴¹, John Q. Trojanowski⁴¹, Lauren Elman⁴², Leo McCluskey⁴², Nazli Basak⁴³, Thomas Meitinger⁴⁴, Peter Lichtner⁴⁴, Milena Blagojevic-Radivojkovic⁴⁴, Christian R. Andres⁴⁵, Cindy Maurel⁴⁵, Gilbert Bensimon⁴⁶, Bernhard Landwehrmeyer⁴⁷, Alexis Brice⁴⁸, Christine A.M. Payan⁴⁶, Safa Saker-Delye⁴⁹, Alexandra Dürr⁵⁰, Nicholas Wood⁵¹, Lukas Tittmann⁵², Wolfgang Lieb⁵², Andre Franke⁵³, Marcella Rietschel⁵⁴, Sven Cichon^{55,56,57,58,59}, Markus M. Nöthen^{55,56}, Philippe Amouyel⁶⁰, Christophe Tzourio⁶¹, Jean-François Dartigues⁶¹, Andre G. Uitterlinden^{62,63}, Fernando Rivadeneira^{62,63}, Karol Estrada⁶², Albert Hofman⁶³, Charles Curtis⁶⁴, Anneke J. van der Kooij¹⁵, Marianne de Visser¹⁵, Markus Weber⁶⁵, Christopher E. Shaw⁸, Bradley N. Smith⁸, Orietta Pansarasa⁶⁶, Cristina Cereda⁶⁶, Roberto Del Bo⁶⁷, Giacomo P. Comi⁶⁷, Sandra D'Alfonso⁶⁸, Cinzia Bertolin⁶⁹, Gianni Soraru⁶⁹, Letizia Mazzini⁷⁰, Viviana Pensato⁷¹, Cinzia Gellera⁷¹, Cinzia Tiloca¹⁶, Antonia Ratti^{16,17}, Andrea Calvo^{72,73}, Cristina Moglia^{72,73}, Maura Brunetti^{72,73}, Simon Arcuti⁷⁴, Rosa Capozzo⁷⁴, Chiara Zecca⁷⁴, Christian Lunetta⁷⁵, Silvana Penco⁷⁶, Nilo Riva⁷⁷, Alessandro Padovani⁷⁸, Massimiliano Filosto⁷⁸, Ian Blair¹⁰, P. Nigel Leigh⁷⁹, Federico Casale⁷², Adriano Chio^{72,73}, Ettore Beghi⁸⁰, Elisabetta Pupillo⁸⁰, Rosanna Tortelli⁷⁴, Giancarlo Logroscino^{81,82}, John Powell⁸, Albert C. Ludolph⁴⁷, Jochen H. Weishaupt⁴⁷, Wim Robberecht⁸³, Philip Van Damme^{83,84}, Robert H. Brown⁸⁵, Jonathan Glass²⁴, John E. Landers⁸⁵, Peter M. Andersen^{46,86}, Philippe Corcia^{87,88}, Patrick Vourc'h⁴⁵, Vincenzo Silani^{16,17}, Michael A. van Es³, R. Jeroen Pasterkamp⁸⁹, Cathryn M. Lewis^{90,91} & Gerome Breen^{6,92,93}

¹⁰Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Macquarie University, Sydney, New South Wales, Australia. ¹¹University of Sydney, ANZAC Research Institute, Concord Hospital, Sydney, New South Wales, Australia. ¹²The Stacey MND Laboratory, Department of Pathology, The University of Sydney, Sydney, New South Wales, Australia. ¹³Brain and Mind Research Institute, The University of Sydney, New South Wales, Australia. ¹⁴Translational Bioinformatics, Commonwealth Scientific and Industrial Research Organisation, Sydney, New South Wales, Australia. ¹⁵Department of Neurology, Academic Medical Center, Amsterdam, The Netherlands. ¹⁶Department of Neurology and Laboratory of Neuroscience, IRCCS Istituto Auxologico Italiano, Milano, Italy. ¹⁷Department of Pathophysiology and Transplantation, 'Dino Ferrari' Center, Università degli Studi di Milano, Milano, Italy. ¹⁸Institut du Cerveau et de la Moelle épinière, Inserm U1127, CNRS UMR 7225, Sorbonne Universités, UPMC Univ Paris 06 UMR51127, Paris, France. ¹⁹Ramsay Générale de Santé, Hôpital Peupliers, Centre SLA Ile de France, Paris, France. ²⁰Institute of Physiology and Institute of Molecular Medicine, University of Lisbon, Lisbon, Portugal. ²¹Department of Neurosciences, Hospital de Santa Maria-CHLN, Lisbon, Portugal. ²²Department of Neurology, Hospital Carlos III, Madrid, Spain. ²³Neurology Department, Hospital de la Santa Creu i Sant Pau de Barcelona, Autonomous University of Barcelona, Barcelona, Spain. ²⁴Department Neurology and Emory ALS Center, Emory University School of Medicine, Atlanta, Georgia, USA. ²⁵Euan MacDonald Centre for Motor Neurone Disease Research, Edinburgh, UK. ²⁶Centre for Neuroregeneration and Medical Research Council Centre for Regenerative Medicine, University of Edinburgh, Edinburgh, UK. ²⁷School of Clinical and Experimental Medicine, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK. ²⁸Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK. ²⁹Sheffield Institute for Translational Neuroscience (SITraN), University of Sheffield, Sheffield, UK. ³⁰Department of Molecular Neuroscience, Institute of Neurology, University College London, London, UK. ³¹Department of Clinical Neuroscience, Institute of Neurology, University College London, London, UK. ³²Reta Lila Weston Institute, Institute of Neurology, University College London, London, UK. ³³Department of Neurodegenerative Diseases, Institute of Neurology, University College London, London, UK. ³⁴Centre for Neuroscience and Trauma, Blizard Institute, Queen Mary University of London, London, UK. ³⁵North-East London and Essex Regional Motor Neuron Disease Care Centre, London, London, UK. ³⁶Department of Neurology, Medical School Hannover, Hannover, Germany. ³⁷Department of Neurology, Otto-von-Guericke University Magdeburg, Magdeburg, Germany. ³⁸Institute for Clinical Neurobiology, University of Würzburg, Würzburg, Germany. ³⁹Charité University Hospital, Humboldt-University, Berlin, Germany. ⁴⁰Department of Neurology, University of California, San Francisco, California, USA. ⁴¹Center for Neurodegenerative Disease Research, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, USA. ⁴²Department of Neurology, Perelman School of Medicine at the University of Pennsylvania, Pennsylvania, USA. ⁴³Neurodegeneration Research Laboratory, Bogazici University, Istanbul, Turkey. ⁴⁴Institute of Human Genetics, Helmholtz Zentrum München, Neuherberg, Germany. ⁴⁵INSERM U930, Université François Rabelais, Tours, France. ⁴⁶APHP, Département de Pharmacologie Clinique, Hôpital de la Pitié-Salpêtrière, UPMC Pharmacologie, Paris 6, Paris, France. ⁴⁷Department of Neurology, Ulm University, Ulm, Germany. ⁴⁸INSERM U 1127, CNRS UMR 7225, Sorbonne Universités, Paris, France. ⁴⁹Genethon, CNRS UMR 8587 Evry, France.

⁵⁰Department of Medical Genetics, L'Institut du Cerveau et de la Moelle Épinière, Hôpital Salpêtrière, Paris. ⁵¹Department of Neurogenetics, Institute of Neurology, University College London, London, UK. ⁵²PopGen Biobank and Institute of Epidemiology, Christian Albrechts-University Kiel, Kiel, Germany. ⁵³Institute of Clinical Molecular Biology, Kiel University, Kiel, Germany. ⁵⁴Central Institute of Mental Health, Mannheim, Germany; Medical Faculty Mannheim. ⁵⁵Institute of Human Genetics, University of Bonn, Bonn, Germany. ⁵⁶Department of Genomics, Life and Brain Center, Bonn, Germany. ⁵⁷University Hospital Basel, University of Basel, Basel, Switzerland. ⁵⁸Division of Medical Genetics, Department of Biomedicine, University of Basel, Basel, Switzerland. ⁵⁹Institute of Neuroscience and Medicine INM-1, Research Center Juelich, Juelich, Germany. ⁶⁰Lille University, INSERM U744, Institut Pasteur de Lille, Lille, France. ⁶¹Bordeaux University, ISPED, Centre INSERM U897-Epidemiologie-Biostatistique & CIC-1401, CHU de Bordeaux, Pole de Sante Publique, Bordeaux, France. ⁶²Department of Internal Medicine, Genetics Laboratory, Erasmus Medical Center Rotterdam, Rotterdam, The Netherlands. ⁶³Department of Epidemiology, Erasmus Medical Center Rotterdam, Rotterdam, The Netherlands. ⁶⁴MRC Social, Genetic and Developmental Psychiatry Centre, King's College London, London, London, UK. ⁶⁵Neuromuscular Diseases Unit/ALS Clinic, Kantonsspital St Gallen, 9007 St Gallen, Switzerland. ⁶⁶Laboratory of Experimental Neurobiology, IRCCS 'C. Mondino' National Institute of Neurology Foundation, Pavia, Italy. ⁶⁷Neurologic Unit, IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy. ⁶⁸Department of Health Sciences, Interdisciplinary Research Center of Autoimmune Diseases, UPO, Università del Piemonte Orientale, Novara, Italy. ⁶⁹Department of Neurosciences, University of Padova, Padova, Italy. ⁷⁰Department of Neurology, University of Eastern Piedmont, Novara, Italy. ⁷¹Unit of Genetics of Neurodegenerative and Metabolic Diseases, Fondazione IRCCS Istituto Neurologico 'Carlo Besta', Milano, Italy. ⁷²Rita Levi Montalcini' Department of Neuroscience, ALS Centre, University of Torino, Turin, Italy. ⁷³Azienda Ospedaliera Città della Salute e della Scienza, Torino, Italy. ⁷⁴Department of Clinical research in Neurology, University of Bari 'A. Moro', at Pia Fondazione 'Card. G. Panico', Tricase, Italy. ⁷⁵NEMO Clinical Center, Serena Onlus Foundation, Niguarda Ca' Granda Hospital, Milan, Italy. ⁷⁶Medical Genetics Unit, Department of Laboratory Medicine, Niguarda Ca' Granda Hospital, Milan, Italy. ⁷⁷Department of Neurology, Institute of Experimental Neurology (INSPE), Division of Neuroscience, San Raffaele Scientific Institute, Milan, Italy. ⁷⁸University Hospital 'Spedali Civili', Brescia, Italy. ⁷⁹Department of Neurology, Brighton and Sussex Medical School Trafford Centre for Biomedical Research, University of Sussex, Falmer, East Sussex, UK. ⁸⁰Laboratory of Neurological Diseases, Department of Neuroscience, IRCCS Istituto di Ricerche Farmacologiche Mario Negri, Milano, Italy. ⁸¹Department of Basic Medical Sciences, Neuroscience and Sense Organs, University of Bari 'Aldo Moro', Bari, Italy. ⁸²Unit of Neurodegenerative Diseases, Department of Clinical Research in Neurology, University of Bari 'Aldo Moro', at Pia Fondazione Cardinale G. Panico, Tricase, Lecce, Italy. ⁸³Department of Neurology, University Hospital Leuven, Leuven Belgium. ⁸⁴KU Leuven-University of Leuven, Department of Neurosciences, VIB-Vesalius Research Center, Leuven, Belgium. ⁸⁵Department of Neurology, University of Massachusetts Medical School, Worcester, Massachusetts, USA. ⁸⁶Department of Pharmacology and Clinical Neuroscience, Umeå University, Umeå, Sweden. ⁸⁷Centre SLA, CHRU de Tours, Tours, France. ⁸⁸Federation des Centres SLA Tours and Limoges, LITORALS, Tours, France. ⁸⁹Department of Translational Neuroscience, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, The Netherlands. ⁹⁰Department of Genetics, University of Groningen, University Medical Centre Groningen, Groningen, The Netherlands. ⁹¹Department of Medical and Molecular Genetics, King's College London, London, UK. ⁹²loPPN Genomics & Biomarker Core, Translational Genetics Group, MRC Social, Genetic and Developmental Psychiatry Centre, King's College London, London, UK. ⁹³NIHR Biomedical Research Centre for Mental Health, Maudsley Hospital and Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK.

Schizophrenia Working Group of the Psychiatric Genomics Consortium

Stephan Ripke^{94,95}, Benjamin M. Neale^{94,95,96,97}, Aiden Corvin⁹⁸, James T.R. Walters⁹⁹, Kai-How Farh⁹⁴, Peter A. Holmans^{99,100}, Phil Lee^{94,95,97}, Brendan Bulik-Sullivan^{94,95}, David A. Collier^{101,102}, Hailiang Huang^{94,96}, Tune H. Pers^{96,103,104}, Ingrid Agartz^{105,106,107}, Esben Agerbo^{108,109,110}, Margot Albus¹¹¹, Madeline Alexander¹¹², Farooq Amin^{113,114}, Silviu A. Bacanu¹¹⁵, Martin Begemann¹¹⁶, Richard A. Belliveau Jr⁹⁵, Judit Bene^{117,118}, Sarah E. Bergen^{95,119}, Elizabeth Bevilacqua⁹⁵, Tim B. Bigdeli¹¹⁵, Donald W. Black¹²⁰, Richard Bruggeman¹²¹, Nancy G. Buccola¹²², Randy L. Buckner^{123,124,125}, William Byerley¹²⁶, Wiepke Cahn⁴, Guiqing Cai^{127,128}, Dominique Campion¹²⁹, Rita M. Cantor⁵, Vaughan J. Carr^{130,131}, Noa Carrera⁹⁹, Stanley V. Catts^{130,132}, Kimberley D. Chambert⁹⁵, Raymond C.K. Chan¹³³, Ronald Y.L. Chan¹³⁴, Eric Y.H. Chen^{134,135}, Wei Cheng¹³⁶, Eric F.C. Cheung¹³⁷, Siow Ann Chong¹³⁸, C. Robert Cloninger¹³⁹, David Cohen¹⁴⁰, Nadine Cohen¹⁴¹, Paul Cormican⁹⁸, Nick Craddock^{99,100}, James J. Crowley¹⁴², David Curtis^{143,144}, Michael Davidson¹⁴⁵, Kenneth L. Davis¹²⁸, Franziska Degenhardt^{55,56}, Jurgen Del Favero¹⁴⁶, Ditte Demontis^{110,147,148}, Dimitris Dikeos¹⁴⁹, Timothy Dinan¹⁵⁰, Srdjan Djurovic^{107,151}, Gary Donohoe^{98,152}, Elodie Drapeau¹²⁸, Jubao Duan^{153,154}, Frank Dudbridge¹⁵⁵, Naser Durmishi¹⁵⁶, Peter Eichhammer¹⁵⁷, Johan Eriksson^{158,159,160}, Valentina Escott-Price⁹⁹, Laurent Essioux¹⁶¹, Ayman H. Fanous^{162,163,164,165}, Marttilas S. Farrell¹⁴², Josef Frank¹⁶⁶, Lude Franke⁹⁰, Robert Freedman¹⁶⁷, Nelson B. Freimer⁶, Marion Friedl¹⁶⁸, Joseph I. Friedman¹²⁸, Menachem Fromer^{94,95,97,169}, Giulio Genovese⁹⁵, Lyudmila Georgieva⁹⁹, Ina Giegling^{168,170}, Paola Giusti-Rodríguez¹⁴², Stephanie Godard¹⁷¹, Jacqueline I. Goldstein^{94,96}, Vera Golimbet¹⁷², Srihari Gopal¹⁴¹, Jacob Gratten¹⁷³, Lieuwe de Haan¹⁷⁴, Christian Hammer¹¹⁶, Marian L. Hamshere⁹⁹, Mark Hansen¹⁷⁵, Thomas Hansen^{110,176}, Vahram Haroutunian^{128,177,178}, Annette M. Hartmann¹⁶⁸, Frans A. Henskens^{130,179,180}, Stefan Herms^{55,56,58}, Joel N. Hirschhorn^{96,104,181}, Per Hoffmann^{55,56,58}, Andrea Hofman^{55,56}, Mads V. Hollegaard¹⁸², David M. Hougaard¹⁸², Masashi Ikeda¹⁸³, Inge Joa¹⁸⁴, Antonio Julià¹⁸⁵, Luba Kalaydjieva^{186,187}, Sena Karachanak-Yankova¹⁸⁸, Juha Karjalainen⁹⁰, David Kavanagh⁹⁹,

Matthew C. Keller¹⁸⁹, James L. Kennedy^{190,191,192}, Andrey Khrunin¹⁹³, Yunjung Kim¹⁴², Janis Klovins¹⁹⁴, James A. Knowles¹⁹⁵, Bettina Konte¹⁶⁸, Vaidutis Kucinskas¹⁹⁶, Zita Ausrele Kucinskiene¹⁹⁶, Hana Kuzelova-Ptackova^{197,198}, Anna K. Kähler¹¹⁹, Claudine Laurent^{112,199}, Jimmy Lee^{138,200}, S. Hong Lee¹⁷³, Sophie E. Legge⁹⁹, Bernard Lerer²⁰¹, Miaoxin Li^{134,202}, Tao Li²⁰³, Kung-Yee Liang²⁰⁴, Jeffrey Lieberman²⁰⁵, Svetlana Limborska¹⁹³, Carmel M. Loughland^{130,206}, Jan Lubinski²⁰⁷, Jouko Lönnqvist²⁰⁸, Milan Macek^{197,198}, Patrik K.E. Magnusson¹¹⁹, Brion S. Maher²⁰⁹, Wolfgang Maier²¹⁰, Jacques Mallet²¹¹, Sara Marsal¹⁸⁵, Manuel Mattheisen^{110,147,148,212}, Morten Mattingsdal^{107,213}, Robert W. McCarley^{214,215}, Colm McDonald²¹⁶, Andrew M. McIntosh^{217,218}, Sandra Meier¹⁶⁶, Carin J. Meijer¹⁷⁴, Bela Melegh^{117,118}, Ingrid Melle^{107,219}, Raquelle I. Meshulam-Gately^{214,220}, Andres Metspalu²²¹, Patricia T. Michie^{130,222}, Lili Milani²²¹, Vihra Milanova²²³, Younes Mokrab¹⁰¹, Derek W. Morris^{98,152}, Ole Mors^{110,147,224}, Kieran C. Murphy²²⁵, Robin M. Murray²²⁶, Inez Myin-Germeys²²⁷, Bertram Müller-Myhsok^{228,229,230}, Mari Nelis²²¹, Igor Nenadic²³¹, Deborah A. Nertney²³², Gerald Nestadt²³³, Kristin K. Nicodemus²³⁴, Liene Nikitina-Zake¹⁹⁴, Laura Nisenbaum²³⁵, Annelie Nordin²³⁶, Eadbhard O'Callaghan²³⁷, Colm O'Dushlaine⁹⁵, F. Anthony O'Neill²³⁸, Sang-Yun Oh²³⁹, Ann Olincy¹⁶⁷, Line Olsen^{110,176}, Jim Van Os^{227,240}, Christos Pantelis^{130,241}, George N. Papadimitriou¹⁴⁹, Sergi Papiol¹¹⁶, Elena Parkhomenko¹²⁸, Michele T. Pato¹⁹⁵, Tiina Paunio^{242,243}, Milica Pejovic-Milovancevic²⁴⁴, Diana O. Perkins²⁴⁵, Olli Pietiläinen^{243,246}, Jonathan Pimm¹⁴⁴, Andrew J. Pocklington⁹⁹, Alkes Price²⁴⁷, Ann E. Pulver²³³, Shaun M. Purcell¹⁶⁹, Digby Quested²⁴⁸, Henrik B. Rasmussen^{110,176}, Abraham Reichenberg¹²⁸, Mark A. Reimers²⁴⁹, Alexander L. Richards^{99,100}, Joshua L. Roffman^{123,125}, Panos Roussos^{169,250}, Douglas M. Ruderfer¹⁶⁹, Veikko Salomaa¹⁶⁰, Alan R. Sanders^{153,154}, Ulrich Schall^{130,206}, Christian R. Schubert²⁵¹, Thomas G. Schulze^{166,252}, Sibylle G. Schwab²⁵³, Edward M. Scolnick⁹⁵, Rodney J. Scott^{130,254,255}, Larry J. Seidman^{214,220}, Jianxin Shi²⁵⁶, Engilbert Sigurdsson²⁵⁷, Teimuraz Silagadze²⁵⁸, Jeremy M. Silverman^{128,259}, Kang Sim¹³⁸, Petr Slominsky¹⁹³, Jordan W. Smoller^{95,97}, Hon-Cheong So¹³⁴, Chris C. A. Spencer²⁶⁰, Eli A. Stahl^{96,169}, Hreinn Stefansson²⁶¹, Stacy Steinberg²⁶¹, Elisabeth Stogmann²⁶², Richard E. Straub²⁶³, Eric Strengman^{264,265}, Jana Strohmaier¹⁶⁶, T. Scott Stroup²⁰⁵, Mythily Subramaniam¹³⁸, Jaana Suvisaari²⁰⁸, Dragan M. Svrakic¹³⁹, Jin P. Szatkiewicz¹⁴², Erik Söderman¹⁰⁵, Srinivas Thirumalai²⁶⁶, Draga Toncheva¹⁸⁸, Sarah Tosato²⁶⁷, Juha Veijola^{268,269}, John Waddington²⁷⁰, Dermot Walsh²⁷¹, Dai Wang¹⁴¹, Qiang Wang²⁰³, Bradley T. Webb¹¹⁵, Mark Weiser¹⁴⁵, Dieter B. Wildenauer²⁷², Nigel M. Williams²⁷³, Stephanie Williams¹⁴², Stephanie H. Witt¹⁶⁶, Aaron R. Wolen²⁴⁹, Emily H.M. Wong¹³⁴, Brandon K. Wormley¹¹⁵, Hualin Simon Xi²⁷⁴, Clement C. Zai^{190,191}, Xuebin Zheng²⁷⁵, Fritz Zimprich²⁶², Naomi R. Wray¹⁷³, Kari Stefansson²⁶¹, Peter M. Visscher¹⁷³, Rolf Adolfsson²³⁶, Ole A. Andreassen^{107,219}, Douglas H.R. Blackwood²¹⁸, Elvira Bramon²⁷⁶, Joseph D. Buxbaum^{127,128,177,277}, Anders D. Børglum^{110,147,148,224}, Ariel Darvasi²⁷⁸, Enrico Domenici²⁷⁹, Hannelore Ehrenreich¹¹⁶, Tõnu Esko^{96,104,181,221}, Pablo V. Gejman^{153,154}, Michael Gill⁹⁸, Hugh Gurling¹⁴⁴, Christina M. Hultman¹¹⁹, Nakao Iwata¹⁸³, Assen V. Jablensky^{130,280,281,282}, Erik G. Jönsson¹⁰⁵, Kenneth S. Kendler²⁸³, George Kirov⁹⁹, Jo Knight^{190,191,192}, Todd Lencz^{284,285,286}, Douglas F. Levinson¹¹², Qingqin S. Li¹⁴¹, Jianjun Liu^{275,287}, Anil K. Malhotra^{284,285,286}, Steven A. McCarroll^{95,181}, Andrew McQuillin¹⁴⁴, Jennifer L. Moran⁹⁵, Preben B. Mortensen^{108,109,110}, Bryan J. Mowry^{173,288}, Michael J. Owen^{99,100}, Aarno Palotie^{97,246,289}, Carlos N. Pato¹⁹⁵, Tracey L. Petryshen^{214,289,290}, Danielle Posthuma^{291,292,293}, Brien P. Riley²⁸³, Dan Rujescu^{168,170}, Pak C. Sham^{134,135,202}, Pamela Sklar^{169,177,250}, David St Clair²⁹⁴, Daniel R. Weinberger^{263,295}, Jens R. Wendland²⁵¹, Thomas Werge^{110,176,296}, Mark J. Daly⁹⁴, Patrick F. Sullivan^{119,142,245} & Michael C. O'Donovan^{99,100}

⁹⁴Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, Massachusetts, USA. ⁹⁵Stanley Center for Psychiatric Research, Broad Institute of M.I.T. and Harvard, Cambridge, Massachusetts, USA. ⁹⁶Medical and Population Genetics Program, Broad Institute of M.I.T. and Harvard,

Cambridge, Massachusetts, USA. ⁹⁷Psychiatric and Neurodevelopmental Genetics Unit, Massachusetts General Hospital, Boston, Massachusetts, USA. ⁹⁸Neuropsychiatric Genetics Research Group, Department of Psychiatry, Trinity College, Dublin, Ireland. ⁹⁹MRC Centre for Neuropsychiatric Genetics and Genomics, Institute of Psychological Medicine and Clinical Neurosciences, School of Medicine, Cardiff University, Cardiff, UK. ¹⁰⁰National Centre for Mental Health, Cardiff University, Cardiff, Wales. ¹⁰¹Eli Lilly and Company Limited, Erl Wood Manor, Sunninghill Road, Windlesham, Surrey, UK. ¹⁰²Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, King's College London, London, UK. ¹⁰³Center for Biological Sequence Analysis, Department of Systems Biology, Technical University of Denmark, Lyngby, Denmark. ¹⁰⁴Division of Endocrinology and Center for Basic and Translational Obesity Research, Boston Children's Hospital, Boston, Massachusetts, USA. ¹⁰⁵Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden. ¹⁰⁶Department of Psychiatry, Diakonhjemmet Hospital, Oslo, Norway. ¹⁰⁷NORMENT, K.G. Jebsen Centre for Psychosis Research, Institute of Clinical Medicine, University of Oslo, Oslo, Norway. ¹⁰⁸Centre for Integrative Register-based Research, CIRRAU, Aarhus University, Aarhus, Denmark. ¹⁰⁹National Centre for Register-based Research, Aarhus University, Aarhus, Denmark. ¹¹⁰The Lundbeck Foundation Initiative for Integrative Psychiatric Research, iPSYCH, Denmark. ¹¹¹State Mental Hospital, Haar, Germany. ¹¹²Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, California, USA. ¹¹³Department of Psychiatry and Behavioral Sciences, Atlanta Veterans Affairs Medical Center, Atlanta, Georgia, USA. ¹¹⁴Department of Psychiatry and Behavioral Sciences, Emory University, Atlanta, Georgia, USA. ¹¹⁵Virginia Institute for Psychiatric and Behavioral Genetics, Department of Psychiatry, Virginia Commonwealth University, Richmond, Virginia, USA. ¹¹⁶Clinical Neuroscience, Max Planck Institute of Experimental Medicine, Göttingen, Germany. ¹¹⁷Department of Medical Genetics, University of Pécs, Pécs, Hungary. ¹¹⁸Szentagothai Research Center, University of Pécs, Pécs, Hungary. ¹¹⁹Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden. ¹²⁰Department of Psychiatry, University of Iowa Carver College of Medicine, Iowa City, Iowa, USA. ¹²¹University Medical Center Groningen, Department of Psychiatry, University of Groningen, The Netherlands. ¹²²School of Nursing, Louisiana State University Health Sciences Center, New Orleans, Louisiana, USA. ¹²³Athinoula A. Martinos Center, Massachusetts General Hospital, Boston, Massachusetts, USA. ¹²⁴Center for Brain Science, Harvard University, Cambridge Massachusetts, USA. ¹²⁵Department of Psychiatry, Massachusetts General Hospital, Boston, Massachusetts, USA. ¹²⁶Department of Psychiatry, University of California at San Francisco, San Francisco, California, USA. ¹²⁷Department of Human Genetics, Icahn School of Medicine at Mount Sinai, New York, New York, USA. ¹²⁸Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, New York, USA. ¹²⁹Centre Hospitalier du Rouvray and INSERM U1079 Faculty of Medicine, Rouen, France. ¹³⁰Schizophrenia Research Institute, Sydney, Australia. ¹³¹School of Psychiatry, University of New South Wales, New South Wales, Sydney, Australia. ¹³²Royal Brisbane and Women's Hospital, University of Queensland, Queensland, Brisbane, Australia. ¹³³Institute of Psychology, Chinese Academy of Science, Beijing, China. ¹³⁴Department of Psychiatry, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China. ¹³⁵State Ket Laboratory for Brain and Cognitive Sciences, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China. ¹³⁶Department of Computer Science, University of North Carolina, Chapel Hill, North Carolina, USA. ¹³⁷Castle Peak Hospital, Hong Kong, China. ¹³⁸Institute of Mental Health, Singapore. ¹³⁹Department of Psychiatry, Washington University, St Louis, Missouri, USA. ¹⁴⁰Department of Child and Adolescent Psychiatry, Pierre and Marie Curie Faculty of Medicine and Brain and Spinal Cord Institute (ICM), Paris, France. ¹⁴¹Neuroscience Therapeutic Area, Janssen Research and Development, LLC, Raritan, New Jersey, USA. ¹⁴²Department of Genetics, University of North Carolina, Chapel Hill, North Carolina, USA. ¹⁴³Department of Psychological Medicine, Queen Mary University of London, London, UK. ¹⁴⁴Molecular Psychiatry Laboratory, Division of Psychiatry, University College London, London, UK. ¹⁴⁵Sheba Medical Center, Tel Hashomer, Israel. ¹⁴⁶Applied Molecular Genomics Unit, V.I.B. Department of Molecular Genetics, University of Antwerp, Antwerp, Belgium. ¹⁴⁷Centre for Integrative Sequencing, iSEQ, Aarhus University, Aarhus, Denmark. ¹⁴⁸Department of Biomedicine, Aarhus University, Aarhus, Denmark. ¹⁴⁹First Department of Psychiatry, University of Athens Medical School, Athens, Greece. ¹⁵⁰Department of Psychiatry, University College Cork, Ireland. ¹⁵¹Department of Medical Genetics, Oslo University Hospital, Oslo, Norway. ¹⁵²Cognitive Genetics and Therapy Group, School of Psychology and Discipline of Biochemistry, National University of Ireland Galway, Ireland. ¹⁵³Department of Psychiatry and Behavioral Neuroscience, University of Chicago, Chicago, Illinois, USA. ¹⁵⁴Department of Psychiatry and Behavioral Sciences, NorthShore University HealthSystem, Evanston, Illinois, USA. ¹⁵⁵Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, London, UK. ¹⁵⁶Department of Child and Adolescent Psychiatry, University Clinic of Psychiatry, Skopje, Republic of Macedonia. ¹⁵⁷Department of Psychiatry, University of Regensburg, Regensburg, Germany. ¹⁵⁸Department of General Practice, Helsinki University Central Hospital, Helsinki, Finland. ¹⁵⁹Folkhälsan Research Center, Helsinki, Finland. ¹⁶⁰National Institute for Health and Welfare, Helsinki, Finland. ¹⁶¹Translational Technologies and Bioinformatics, Pharma Research and Early Development, F. Hoffman-La Roche, Basel, Switzerland. ¹⁶²Department of Psychiatry, Georgetown University School of Medicine, Washington, District Of Columbia, USA. ¹⁶³Department of Psychiatry, Keck School of Medicine of the University of Southern California, Los Angeles, California, USA. ¹⁶⁴Department of Psychiatry, Virginia Commonwealth University School of Medicine, Richmond, Virginia, USA. ¹⁶⁵Mental Health Service Line, Washington V.A. Medical Center, Washington, District Of Columbia, USA. ¹⁶⁶Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Heidelberg, Germany. ¹⁶⁷Department of Psychiatry, University of Colorado Denver, Aurora, Colorado, USA. ¹⁶⁸Department of Psychiatry, University of Halle, Halle, Germany. ¹⁶⁹Division of Psychiatric Genomics, Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, New York, USA. ¹⁷⁰Department of Psychiatry, University of Munich, Munich, Germany. ¹⁷¹Departments of Psychiatry and Human and Molecular Genetics, INSERM, Institut de Myologie, Hôpital de la Pitié-Salpêtrière, Paris, France. ¹⁷²Mental Health Research Centre, Russian Academy of Medical Sciences, Moscow, Russia. ¹⁷³Queensland Brain Institute, The University of Queensland, Brisbane, Queensland, Australia. ¹⁷⁴Academic Medical Centre University of Amsterdam, Department of Psychiatry, Amsterdam, The Netherlands. ¹⁷⁵llumina, Inc., La Jolla, California, USA. ¹⁷⁶Institute of Biological Psychiatry, M.H.C. Sct. Hans, Mental Health Services, Copenhagen, Denmark. ¹⁷⁷Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, New York, USA. ¹⁷⁸JJ Peters V.A. Medical Center, Bronx, New York, USA. ¹⁷⁹Priority Research Centre for Health Behaviour, University of Newcastle, Newcastle, Australia. ¹⁸⁰School of Electrical Engineering and Computer Science, University of Newcastle, Newcastle, Australia. ¹⁸¹Department of Genetics, Harvard Medical School, Boston, Massachusetts, USA. ¹⁸²Section of Neonatal Screening and Hormones, Department of Clinical Biochemistry, Immunology and Genetics, Statens Serum Institut, Copenhagen, Denmark. ¹⁸³Department of Psychiatry, Fujita Health University School of Medicine, Toyoake, Aichi, Japan. ¹⁸⁴Regional Centre for Clinical Research in Psychosis, Department of Psychiatry, Stavanger University Hospital, Stavanger, Norway. ¹⁸⁵Rheumatology Research Group, Vall d'Hebron Research Institute, Barcelona, Spain. ¹⁸⁶Centre for Medical Research, The University of Western Australia, Perth, Western Australia, Australia. ¹⁸⁷Perkins Institute for Medical Research, The University of Western Australia, Perth, Western Australia, Australia. ¹⁸⁸Department of Medical Genetics, Medical University, Sofia, Bulgaria. ¹⁸⁹Department of Psychology, University of Colorado Boulder, Boulder, Colorado, USA. ¹⁹⁰Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, Ontario, Canada. ¹⁹¹Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada. ¹⁹²Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada. ¹⁹³Institute of Molecular Genetics, Russian Academy of Sciences, Moscow, Russia. ¹⁹⁴Latvian Biomedical Research and Study Centre, Riga, Latvia. ¹⁹⁵Department of Psychiatry and Zilkha Neurogenetics Institute, Keck School of Medicine at University of Southern California, Los Angeles, California, USA. ¹⁹⁶Faculty of Medicine, Vilnius University, Vilnius, Lithuania. ¹⁹⁷Second Faculty of Medicine and University Hospital Motol, Prague, Czech Republic. ¹⁹⁸Department of Biology and Medical Genetics, Charles University Prague, Prague, Czech Republic. ¹⁹⁹Pierre and Marie Curie Faculty of Medicine, Paris, France. ²⁰⁰Duke-NUS Graduate Medical School, Singapore. ²⁰¹Department of Psychiatry, Hadassah-Hebrew University Medical Center, Jerusalem, Israel. ²⁰²Centre for Genomic Sciences, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China. ²⁰³Mental Health Centre and Psychiatric Laboratory, West China Hospital, Sichuan University, Chendu, Sichuan, China. ²⁰⁴Department of Biostatistics, Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland, USA. ²⁰⁵Department of Psychiatry, Columbia University, New York,

New York, USA. ²⁰⁶Priority Centre for Translational Neuroscience and Mental Health, University of Newcastle, Newcastle, Australia. ²⁰⁷Department of Genetics and Pathology, International Hereditary Cancer Center, Pomeranian Medical University in Szczecin, Szczecin, Poland. ²⁰⁸Department of Mental Health and Substance Abuse Services, National Institute for Health and Welfare, Helsinki, Finland. ²⁰⁹Department of Mental Health, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland, USA. ²¹⁰Department of Psychiatry, University of Bonn, Bonn, Germany. ²¹¹Centre National de la Recherche Scientifique, Laboratoire de Génétique Moléculaire de la Neurotransmission et des Processus Neurodégénératifs, Hôpital de la Pitié Salpêtrière, Paris, France. ²¹²Department of Genomics Mathematics, University of Bonn, Bonn, Germany. ²¹³Research Unit, Sørlandet Hospital, Kristiansand, Norway. ²¹⁴Department of Psychiatry, Harvard Medical School, Boston, Massachusetts, USA. ²¹⁵Virginia Boston Health Care System, Brockton, Massachusetts, USA. ²¹⁶Department of Psychiatry, National University of Ireland Galway, Ireland. ²¹⁷Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK. ²¹⁸Division of Psychiatry, University of Edinburgh, Edinburgh, UK. ²¹⁹Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway. ²²⁰Massachusetts Mental Health Center Public Psychiatry Division of the Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA. ²²¹Estonian Genome Center, University of Tartu, Tartu, Estonia. ²²²School of Psychology, University of Newcastle, Newcastle, Australia. ²²³First Psychiatric Clinic, Medical University, Sofia, Bulgaria. ²²⁴Department P, Aarhus University Hospital, Risskov, Denmark. ²²⁵Department of Psychiatry, Royal College of Surgeons in Ireland, Ireland. ²²⁶King's College London, London, UK. ²²⁷Maastricht University Medical Centre, South Limburg Mental Health Research and Teaching Network, EURON, Maastricht, The Netherlands. ²²⁸Institute of Translational Medicine, University Liverpool, UK. ²²⁹Max Planck Institute of Psychiatry, Munich, Germany. ²³⁰Munich Cluster for Systems Neurology (SyNergy), Munich, Germany. ²³¹Department of Psychiatry and Psychotherapy, Jena University Hospital, Jena, Germany. ²³²Department of Psychiatry, Queensland Brain Institute and Queensland Centre for Mental Health Research, University of Queensland, Brisbane, Queensland, Australia. ²³³Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA. ²³⁴Department of Psychiatry, Trinity College Dublin, Dublin, Ireland. ²³⁵Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana, USA. ²³⁶Department of Clinical Sciences, Psychiatry, Umeå University, Umeå, Sweden. ²³⁷DETECT Early Intervention Service for Psychosis, Blackrock, Dublin, Ireland. ²³⁸Centre for Public Health, Institute of Clinical Sciences, Queens University Belfast, Belfast, UK. ²³⁹Lawrence Berkeley National Laboratory, University of California at Berkeley, Berkeley, California, USA. ²⁴⁰Institute of Psychiatry at King's College London, London, UK. ²⁴¹Melbourne Neuropsychiatry Centre, University of Melbourne & Melbourne Health, Melbourne, Australia. ²⁴²Department of Psychiatry, University of Helsinki, Finland. ²⁴³Public Health Genomics Unit, National Institute for Health and Welfare, Helsinki, Helsinki, Finland. ²⁴⁴Medical Faculty, University of Belgrade, Belgrade, Serbia. ²⁴⁵Department of Psychiatry, University of North Carolina, Chapel Hill, North Carolina, USA. ²⁴⁶Institute for Molecular Medicine Finland, FIMM, Helsinki, Finland. ²⁴⁷Department of Epidemiology, Harvard University, Boston, Massachusetts, USA. ²⁴⁸Department of Psychiatry, University of Oxford, Oxford, UK. ²⁴⁹Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Richmond, Virginia, USA. ²⁵⁰Institute for Multiscale Biology, Icahn School of Medicine at Mount Sinai, New York, New York, USA. ²⁵¹PharmaTherapeutics Clinical Research, Pfizer Worldwide Research and Development, Cambridge, Massachusetts, USA. ²⁵²Department of Psychiatry and Psychotherapy, University of Göttingen, Göttingen, Germany. ²⁵³Psychiatry and Psychotherapy Clinic, University of Erlangen, Erlangen, Germany. ²⁵⁴Hunter New England Health Service, Newcastle, Australia. ²⁵⁵School of Biomedical Sciences, University of Newcastle, Newcastle, Australia. ²⁵⁶Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland, USA. ²⁵⁷University of Iceland, Landspítali, National University Hospital, Reykjavik, Iceland. ²⁵⁸Department of Psychiatry and Drug Addiction, Tbilisi State Medical University (TSMU), Tbilisi, Georgia. ²⁵⁹Research and Development, Bronx Veterans Affairs Medical Center, New York, New York, USA. ²⁶⁰Wellcome Trust Centre for Human Genetics, Oxford, UK. ²⁶¹deCODE Genetics, Reykjavik, Iceland. ²⁶²Department of Clinical Neurology, Medical University of Vienna, Vienna, Austria. ²⁶³Lieber Institute for Brain Development, Baltimore, Maryland, USA. ²⁶⁴Department of Medical Genetics, University Medical Centre, Utrecht, The Netherlands. ²⁶⁵Rudolf Magnus Institute of Neuroscience, University Medical Centre Utrecht, Utrecht, The Netherlands. ²⁶⁶Berkshire Healthcare N.H.S. Foundation Trust, Bracknell, UK. ²⁶⁷Section of Psychiatry, University of Verona, Verona, Italy. ²⁶⁸Department of Psychiatry, University of Oulu, Oulu, Finland. ²⁶⁹University Hospital of Oulu, Oulu, Finland. ²⁷⁰Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland, Dublin, Ireland. ²⁷¹Health Research Board, Dublin, Ireland. ²⁷²Department of Psychiatry and Clinical Neurosciences, School of Psychiatry and Clinical Neurosciences, Queen Elizabeth I.I. Medical Centre, Perth, Western Australia, Australia. ²⁷³Department of Psychological Medicine and Neurology, M.R.C. Centre for Neuropsychiatric Genetics and Genomics, School of Medicine, Cardiff University, Cardiff, Wales, UK. ²⁷⁴Computational Sciences CoE, Pfizer Worldwide Research and Development, Cambridge, Massachusetts, USA. ²⁷⁵Human Genetics, Genome Institute of Singapore, Singapore. ²⁷⁶University College London, London, UK. ²⁷⁷Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, New York, USA. ²⁷⁸Department of Genetics, The Hebrew University of Jerusalem, Jerusalem, Israel. ²⁷⁹Neuroscience Discovery and Translational Area, Pharma Research and Early Development, F. Hoffman-La Roche, Basel, Switzerland. ²⁸⁰School of Psychiatry and Clinical Neurosciences, The University of Western Australia, Perth, Australia. ²⁸¹The Perkins Institute of Medical Research, Perth, Australia. ²⁸²UWA Centre for Clinical Research in Neuropsychiatry. ²⁸³Virginia Institute for Psychiatric and Behavioral Genetics, Departments of Psychiatry and Human and Molecular Genetics, Virginia Commonwealth University, Richmond, Virginia, USA. ²⁸⁴The Feinstein Institute for Medical Research, Manhasset, New York, USA. ²⁸⁵The Hofstra NS-LIJ School of Medicine, Hempstead, New York, USA. ²⁸⁶The Zucker Hillside Hospital, Glen Oaks, New York, USA. ²⁸⁷Saw Swee Hock School of Public Health, National University of Singapore, Singapore. ²⁸⁸Queensland Centre for Mental Health Research, University of Queensland, Brisbane, Queensland, Australia. ²⁸⁹The Broad Institute of M.I.T. and Harvard, Cambridge, Massachusetts, USA. ²⁹⁰Center for Human Genetic Research and Department of Psychiatry, Massachusetts General Hospital, Boston, Massachusetts, USA. ²⁹¹Department of Child and Adolescent Psychiatry, Erasmus University Medical Centre, Rotterdam, The Netherlands. ²⁹²Department of Complex Trait Genetics, Neuroscience Campus Amsterdam, V.U. University Medical Center Amsterdam, Amsterdam, The Netherlands. ²⁹³Department of Functional Genomics, Center for Neurogenomics and Cognitive Research, Neuroscience Campus Amsterdam, VU University, Amsterdam, The Netherlands. ²⁹⁴University of Aberdeen, Institute of Medical Sciences, Aberdeen, Scotland, UK. ²⁹⁵Departments of Psychiatry, Neurology, Neuroscience and Institute of Genetic Medicine, Johns Hopkins School of Medicine, Baltimore, Maryland, USA. ²⁹⁶Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark.